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BREAST ABSCESS TREATED WITH 'ALTAFUR': REPORT OF A CLINICAL TRIAL

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The development of antibiotic-resistant varieties of staphylococcus pyogenes has led to a great strain being thrown on to the casualty department of this hospital which, in common with other hospitals all over the world, is having to contend with more and more cases of infection with this resistant organism.

Our attention has recently been directed to a synthetic chemical antibacterial agent of the nitrofuran group of which reports have been made available[1] and for which it has been claimed that it has antibacterial activity on almost 100% of these organisms. An experimental trial of furaltadone, the drug in question, is here presented. Furaltadone, under the trade name of 'altafur' was used throughout the experiment and a preliminary series of tests confirmed that most staphylococci were sensitive to the drug *in vitro*. In the dosage advised, few side-effects or harmful reactions were expected and this we can confirm.

In this hospital we are at present meeting a large number of cases of breast abscess attending for treatment. The majority of these occur in women delivered at the various maternity homes and hospitals in the neighbourhood and a small proportion (about 25%) occur in patients delivered at home. An analysis of the frequency of infection by one of us (J.A.E.)[2] shows that almost invariably those who come in from maternity homes and hospitals are infected with 'hospital' staphylococci whereas the cases delivered at home are infected with 'wild' staphylococci which respond readily to most of the commoner antibiotics.

It soon became apparent that the lactational breast abscess was as a rule caused by *Staphylococcus pyogenes aureus* and sensitivity tests were carried out on a large number of cases by the bacteriology department. Only 1 case was found whose staphylococci did not, *in vitro*, respond to furaltadone.[a]

The treatment of these cases presented a real problem. Recurrences, prolonged drainage of pus, repeated visits and many dressings, all combine to make the condition a trying one both for the surgeon and the patient. The amount of time and material used in a busy casualty department treating up to 12 new cases of the condition a week made the organizational side of the matter alone a very difficult one. Maintaining adequate drainage in so many cases was in itself a problem which required careful consideration and is discussed elsewhere.[2]

Our policy has hitherto been to incise the abscess as soon after diagnosis as possible and not to use antibiotics before incision. We have been well aware of the complications associated with the breast abscess treated for a longer or a shorter time with antibiotics. The painful, indurated, pus-filled breasts, with multiple fistulae and secreting tissues almost completely destroyed, are still occasionally encountered in cases coming in from outside and treated ineffectively with penicillin and other antibiotics.

As a first experiment it was resolved to try the effect of 'altafur' (orally administered) on 20 consecutive cases without incision and drainage. No dramatic results were expected because we believed that, unless the pus is evacuated, healing is unlikely to take place, since a drug is theoretically not able to sterilize the avascular core of an abscess. However, in spite of the unorthodox form of this treatment, 6 of the cases subsided without further treatment (Table I).

TABLE I. CASES TREATED WITH 'ALTAFUR' ALONE

Name	*Place of Delivery*	*Age of Child (weeks)*	*Duration of Abscess*	*Lactating*	*Result*
1. S.H.	H	3	1 week	+	*
2. F.J.	M	5	2 weeks	—	I and D
3. K. du P. ..	H	4	1 week	—	I and D
4. F.O.	M	3	1 week	—	I and D
5. A.W.	M	4	1 week	+	I and D
6. V.K.	M	3	2 weeks	—	I and D
7. D.P.	M	4	1 day	+	Resolved
8. M.B.	M	3	2 weeks	+	I and D
9. C.P.	H	4	2 weeks	+	Resolved
10. A.H.	H	8	1 week	+	Absconded
11. W.B.	H	4	1 day	—	I and D
12. M.W.	M	52	2 days	—	Absconded
13. S.V.	H	5	3 weeks	—	I and D
14. S.A.	—	—	4 days	—	I and D
15. G.E.	H	12	5 days	—	Absconded
16. H. v.d. B. ..	—	3	6 days	+	I and D
17. S.S.	—	—	5 days	—	Resolved
18. A.G.	M	3	4 days	+	†
19. R.J.	M	4	2 weeks	—	Resolved
20. M.W.	M	2	3 days	+	Resolved

* Discharged spontaneously; healed in 14 days. † Vomited; drug stopped. I and D—Incision and drainage. H—At home. M—Maternity home or hospital.

All 6 lost their pain within 48 hours and, under daily observation, improvement was constant and maintained. The tender mass lost a great deal of its tenderness but could still be felt several weeks later. Lactation, in those cases who had lactated, continued uninterruptedly and the patients were finally discharged within 3 - 4 weeks.

Those cases which showed no signs of subsiding within 48 hours, or in which improvement was not continuously maintained, were subjected to incision and drainage in the ordinary way and behaved like other breast abscesses; the average healing time was a little shorter than usual—about 28 days.

One single case (S.H.) in the series proved interesting. The abscess opened spontaneously and discharged close to the nipple on the first day of treatment. The whole inflammatory process was over with complete healing within 14 days, leaving a soft, supple breast with almost no residual induration. The hint could hardly have been given in a broader way.

Even a success rate of 30% without operation in an unselected series of cases could be considered only a single step in the proper direction. The next series of cases were therefore treated on more orthodox lines.

In this next group (20 cases, Table II), incision and drainage was performed on the very same day the patient came up for treatment and 'altafur' was started simultaneously.

TABLE II. CASES TREATED WITH INCISION AND DRAINAGE PLUS 'ALTAFUR'

Name	Place of Delivery	Age of Child (weeks)	Duration of Illness (weeks)	Lactating	Healing time (days)	No. of Visits
1. H.S. ..	M	4	2	+	17	1+4
2. S.F. ..	M	4	2	+	10	1+3
3. L.S. ..	M	4	2	+	10	1+3
4. M.J. ..	H	6	2	+	28	1+7
5. D.M. ..	H	52	1	+	19	1+5
6. E.P. ..	M	4	1	+	16	1+5
7. R.R. ..	H	12	4	+	14	1+3
8. E.E. ..	M	12	6	+	19	1+4
9. E.D. ..	M	11	4	+	15	1+5
10. M.A. ..	H	3	½	+	21	1+5
11. A.C. ..	H	10	½	+	13	1+4
12. G.T. ..	M	4	1	—	22	1+7
13. H.K. ..	M	6	2	+	14	1+5
14. J.A. ..	H	4	3	+	21	1+5
15. E.H. ..	M	3	1	+	15	1+4
16. M.S. ..	H	52	3	—	13	1+5
17. J.H. ..	H	7	1	+	19	1+4
18. J.E. ..	M	4	2	+	21	1+7
19. G.O. ..	H	6	2	+	10	1+4
20. S.K. ..	H	4	1	—	6	1+3
Average					16	5

H—At home. M—Maternity home or hospital.
Number of visits—Original for incision and drainage, and number of subsequent visits.

The incision used was a small one, just large enough to admit the forefinger to enable the operator to break down all loculi. A small corrugated rubber drain was stitched in. The patient was instructed to return 48 hours later and was thereafter seen once a week.

The results of this therapy were very satisfactory; purulent discharge ceased within 3 - 4 days. The drain was removed a few days later and the average healing time was 16 days. More remarkable was the sudden loss of pain and tenderness in the breast and the feeling of normal well-being that was quickly restored. The average number of visits after incision and drainage dropped to 5 and very little residual induration was left in the breast, so that within the stated time a soft, painless breast had resulted. In our minds there was no doubt that the infection had been overwhelmed and that a swift resolution had occurred.

Lactation

Robertson, Hansen and Moodie,[3] reporting recently on the incidence and management of gastro-enteritis, a very common disease in non-European babies, have stated as follows: 'In a series of normal non-European infants attending child welfare clinics, it was found that 88% were feeding at the breast at 3 months . . . . in the whole Coloured population of Cape Town 39% of the mothers of young infants return to work soon after the infant's birth . . . . Once breast feeding is discontinued factors are seen to promote malnutrition'. They conclude that 'Promotion of breast feeding, which is the surest safeguard against malnutrition and gastro-enteritis in infancy . . . . can best be encouraged by sympathetic propaganda . . . . at pre- and post-natal clinics'.

The majority of our cases were non-European women of hospital class and we felt that, for the sake of the babies, lactation should not be interrupted if at all possible. No steps were taken to suppress lactation and the patients were instructed to continue feeding with both breasts if possible and certainly with the normal breast. A large proportion continued lactation uninterrupted by the treatment. No untoward effects on the babies were noted. Some of the infants were reported to be a little off their food for the first few days but none of the mothers had to discontinue lactation because the child refused to suck.

Side-reactions

The following were the only side-effects noted in the 40 cases:

Vomiting. This was noted on 3 occasions but, following instructions to take food with the tablets, all but 1 patient were able to continue the treatment. In the single case symptoms ceased on discontinuance of the drug.

Antabuse effect. One of the known side-effects of altafur is that headache, nausea and vomiting occur if alcohol is taken during the course of treatment. The effect is similar to that achieved when antabuse is taken to discourage alcoholism. Since our lactating women do not, as a rule, take alcohol, this side-reaction occurred only once in our series, in a European patient who had not been warned. She continued her course of treatment after due warning.

Skin reactions. None occurred in this particular group of patients, but a single case of an allergic papular skin reaction was observed in a patient treated for a septic hand. This subsided promptly on discontinuing the drug.

Organization

It was now possible to organize the treatment of these cases on a reasonable basis. The following scheme of treatment was adopted:

1. Incise and drain under general anaesthesia on the day of the first visit or as soon thereafter as conveniently possible.
2. The incision should be radial and just large enough to admit the forefinger; break down all loculi.
3. Send a specimen of the pus to the laboratory for sensitivity tests.
4. Stitch in a single corrugated rubber drain.
5. Place on 'altafur', 2 *statim*; then 1 every 6 hours. Dispense 50 tablets (250 mg. each).
6. Inspect in 48 hours; remove drain.
7. See every Wednesday morning thereafter.

Discussion

There has been a great reduction in the duration of the disease, as well as in the number of visits required, when 'altafur' was used in the treatment of lactational breast abscess (Table III). This compares very well with a recent series from Edinburgh.[4] Even more striking, however,

TABLE III. DURATION OF DISEASE

	Incision and drainage	Incision and drainage plus antibiotic	Incision and drainage plus 'altafur'
Number of days from incision to healing	26	31	16
Number of visits	9·5	11	5

has been the rapid restoration of the turgid, tender and swollen breast to a normal, supple and functioning organ. The complete absence of reactions in the babies and the relative insignificance of such few reactions as occurred in the patients themselves, is also gratifying. The number of recurrences has also been comparatively small.

As a result of these findings, we have continued using this drug in the identical way on a further 95 cases, making a total of 135 cases in all. A solitary instance of staphylococcus not sensitive to altafur has been encountered, but

the results and duration of the disease have not in any way altered and the findings detailed above are confirmed and require no modification.

SUMMARY

1. The results of a clinical trial of furaltadone ('altafur') are presented.

2. 20 cases of lactational breast abscess were treated with 'altafur' alone, with resolution in 30%.

3. 20 cases of breast abscess were treated with incision and drainage plus 'altafur'. The time of drainage, length of convalescence, and number of visits, were all significantly reduced. A further 95 cases confirm these findings.

4. An extended trial of this preparation in staphylococcal infections appears justified.

We wish to thank Messrs. SKF Laboratories (Pty.) Ltd. for a generous trial sample of 'altafur', their brand of furaldatone. Dr. J. G. Burger, Medical Superintendent, Groote Schuur Hospital, is thanked for permission to use the cases at this hospital for the clinical trial and Prof. J. H. Louw and Prof. A. Kipps for their interest and cooperation.

REFERENCES

1. Kefauver, D. F., Paberzs, I. and McNamara, T. F. (1959): *Antibiotic Annual 1958 - 1959*, p. 81. New York: Medical Encyclopedia Inc.
2. Engelbrecht, J. A. In the press.
3. Robertson, I., Hansen, J. D. L. and Moodie, A. (1960): S. Afr. Med. J., **34**, 338.
4. Knight, I. C. S. and Nolan, B. (1959): Brit. Med. J., **1**, 1224.

BLADDER CATHETERIZATION WITHOUT DIRECT CONTACT WITH THE URETHRAL CANAL.

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The frequency of infections of the urinary tract and the high incidence of asymptomatic pyelonephritis in the general population have been stressed by various authors.[1-3]

Studies have shown that there is always some danger of introducing infection into the urinary bladder with catheterization.[2,4,5] Nevertheless, if quantitative bacterial counts are performed on properly collected, clean-voided specimens of urine, a diagnosis, including that of inapparent infection, can be made without the risk of introducing bacteria into the bladder.[2,3,6-10]

In the present series of sterile bladder catheterization without direct contact with the urethral canal, investigations have been carried out in an attempt to assess the value of this procedure.

MATERIALS AND METHOD

The series consisted of 51 unselected gynaecological patients at the King Edward VIII Hospital, Durban. Of these, 49 had undergone minor vaginal surgery for various conditions, such as dilatation and curettage and cauterization of the cervix, evacuation of products of conception after incomplete abortion, etc. The other 2 patients had undergone no operative procedure, 1 being a case of threatened abortion and 1 having being sent back from the theatre before the performance of a diagnostic dilatation and curettage because of a watery defaecation. Most of the patients had undergone one or more deliveries. In most of the cases there was a history of previous urinary infection. Urinary symptoms (burning or frequency) were present in 11 out of 30 of the cases; 16 patients were on penicillin, penicillin *plus* streptomycin, penicillin *plus* sulphatriad, or sulphatriad alone.

At all the operations for catheterization, the vulva and vagina were swabbed with a solution of cetavlon, followed by a solution of acriflavin in water. The labia minora were separated with one hand and the external urethral opening swabbed again, in one stroke, with acriflavin solution and immediately dried, usually with another stroke of a sterile gauze. Then a throat swab was inserted at least 1 cm. into the urethra and rolled slightly. From these swabs cultures were taken, and also smears for examination, direct and Gram stained.

A straight chromium-plated tube corresponding to a size-18 Foley catheter was inserted into the bladder, after which the bladder was emptied by passing a whistle-tip rubber catheter through the metal catheter. Suprapubic pressure was often applied, because the patients had urinated not long before the operation. Spilling not infrequently took place between the two catheters, especially when thin rubber catheters were used, and care was taken that only the urine from the rubber catheters was collected. The urine was investigated by examination of the centrifuged deposit (unstained and Gram stained) and by culture.

After the specimen of urine had been collected, the tip of the rubber catheter was stroked as thoroughly as possible on solidified blood-agar and McConkey culture media in Petri dishes. The metal catheter which thus served as a sheath was then removed and its tip cultured in the same way.

All specimens were kept at room temperature and they were usually taken to the laboratory for microscopic and culture examinations within 1 - 2 hours.

On 2 occasions it was necessary to dilate the urethra on account of the size of the metal catheter.

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LABORATORY FINDINGS

Urethral Swabs

On direct examination of the smears from the urethral swabs, pus cells, scanty to moderate in number, were present in 3 of the 51 cases. In these 3, no organisms were seen and the cultures from the swabs were negative. Of the corresponding 3 urinary specimens scanty pus cells were found in 2, with no growth on culture; and numerous pus cells plus trichomonas in the 3rd, with no growth. No cultures were obtained from the metal and rubber catheter tips in these 3 cases.

On Gram staining the smears from the urethral swabs Gram-positive bacilli in moderate numbers, including Döderlein bacilli, were present in 1 case, and no growth was obtained from the swab. Altogether, Döderlein bacilli were seen in the smears from the swabs in 5 cases. In these 5 cases no pus cells were observed in the swabs and the swab cultures were negative.

A moderate growth of *B. coli* was present in culture from the urethral swabs in 1 case, from which also no leucocytes or organisms were observed on examination of the unstained and Gram-stained smears. In this case, which was that of a pregnant patient who did not come to operation, *B. coli* were also found in the cultures from the urine and from both catheters, and moderate amounts of *Trichomonas vaginalis* and Gram-negative bacilli were seen on direct examination of the urine.

Urine

On microscopical examination of the centrifugal deposits from the urine specimens the following results were obtained:

Red blood cells were present in the specimens from 20 of the 51 cases, and of these 20 they were in moderate quantity in 9 and numerous in 5. There was no correlation between red blood cells and pus cells from the same specimen. Red blood cells *plus* pus cells in different amounts were present in 11 specimens.

In 3 specimens containing red blood cells (scanty in 2 and numerous in 1) trichomonas was also present.

Leucocytes were present in 29 of the urine specimens—numerous in 5 and in moderate numbers in 3.

Schistosoma haematobium was present in 1 specimen, associated with scanty pus cells and a moderate number of red blood cells.

Trichomonas vaginalis was present in 8 specimens. In 4 this was associated with 10 or more pus cells per high-power field, in 2 with 5 or more pus cells per field, and in 2 with no pus cells but varying numbers of red blood cells.

Gram-negative bacilli were present in 6 specimens. In 3 of these, all containing pus cells, and 2 also containing trichomonas, the bacilli were scanty. In the other 3 specimens the bacilli were present in moderate numbers; 2 of them contained numerous pus cells and trichomonas and gave on culture a growth of *B. coli* (scanty in one and moderate in the other); the 3rd contained scanty pus cells and a moderate number of red blood cells, and gave no growth on culture.

These growths of *B. coli* were the only growths obtained from the urine on culture. As stated, they were from 2 specimens, which were both associated with trichomonas, numerous pus cells, and Gram-negative bacilli in moderate numbers.

Catheters

The tips of the rubber catheter gave on culture a scanty growth of *B. coli* in 1 case and a moderate growth of *B. coli* in another. Both of these specimens were associated with corresponding *B. coli* culture in the urine.

From the case in which a moderate growth of *B. coli* was obtained from the rubber catheter, the metal catheter also gave a moderate growth of *B. coli*. In the other case in which a growth of *B. coli* (scanty) was obtained from the rubber catheter, the metal catheter gave no growth. In one other case, in which no growth was obtained from the rubber catheter, the metal catheter gave a very scanty growth of *B. coli*; in this case no growth of *B. coli* was obtained from any other specimen from the patient, and the growth from the metal catheter was thought to be due to contamination.

B. coli Cultures

In the following Table the other findings are shown in the 4 cases in which a growth of *B. coli* was obtained on culture:

Urethral Swab		*Urine*					*Rubber Cath.*	*Metal Cath.*
Dir.	*Cult. B. coli*	*RBC*	*Trich. vag.*	*Pus*	*Gram Org.*	*Cult. B. coli*	*Cult. B. coli*	*Cult. B. coli*
—	+	—	+	+++	+	+	+	+
—	—	—	+	+++	+	± f	± f	—
—	—	—	—	—	—	—	—	±
—	—	—	—	±	—	± f	—	—

Nil —. Scanty ±. Moderate + (5 - 9 per H.P. field). Marked +++. Coliform bacilli f.

DISCUSSION AND CONCLUSION

The non-pathogenic Döderlein bacillus was present in 5 of the urethral swabs. The urine and catheter-tip specimens from these 5 patients were negative. They were given no antimicrobial treatment.

In one of the cases in the series (a pregnant primipara, grav. 2) a moderate growth of *B. coli* was obtained from all 4 specimens (urethral swab, urine, and catheter tips). She was a case of pyuria and *Trichomonas vaginalis* infestation of the bladder. She had received no treatment before the investigation, and she did not come to operation.

Pyuria was present in 8 patients, in 6 of which it was associated with *Trichomonas vaginalis* infestation of the bladder; in 2 of the 6, cultures of *B. coli* were obtained. The 2 cases of pyuria not associated with *Trichomonas vaginalis* were cases of septic incomplete abortion and pelvic infection. Both were on penicillin and sulphatriad.

Trichomona vaginalis was present in 8 of the urinary specimens, of which 1 contained numerous red blood cells, 2 scanty red blood cells, and 5 none at all. The association of pyuria and trichomonas was noticeable.

The culture experiments with the tips of the 2 catheters used in the sterile bladder catheterization showed no advantage to be obtained by passing an inner catheter through another catheter as a shield to prevent contact of the inner catheter with the urethra. The one instance in which a very scanty growth of *B. coli* was obtained on culture from the metal tip, without any abnormal findings in the other 3 specimens, was thought to be most probably due to contamination.

SUMMARY

An investigation into bladder catheterization without direct contact with the urethral canal was made on 51 unselected gynaecological patients at the King Edward VIII Hospital.

Urethral swabs were taken, after which the urine was withdrawn by means of a rubber catheter passed through a metal catheter already inserted into the urethra, so as to prevent contact of the rubber catheter with the urethra.

Bacteriological investigations were carried out on the urethral swabs, the urine specimens, and the tips of both the metal and rubber catheters.

No advantage in sterile bladder catheterization by thus preventing the catheter from coming into contact with the urethra could be found in this small series of cases.

I should like to thank Prof. Derk Crichton of the Department of Obstetrics and Gynaecology, King Edward VIII Hospital, and the University of Natal, for his encouragement and advice, and Dr. Kenneth Watson and Miss Ethel Bennett of the Pathology Department, who carried out the bacteriological investigations.

REFERENCES

1. Kass, E. H. (1956): Trans. Assoc. Amer. Phycns, **69**, 56.
2. *Idem* (1955): Amer. J. Med., **18**, 764.
3. Sanford, J. P. (1959): J. Amer. Med. Assoc., **169**, 1711.
4. Beeson, P. B. (1955): Yale J. Biol. Med., **28**, 81.
5. Guze, L. B. and Beeson, P. B. (1956): New Engl. J. Med., **255**, 474.
6. Boshell, B. R. and Sanford, J. P. (1958): Ann. Intern. Med., **48**, 1040.
7. Marple, C. D. (1941): *Ibid.*, **14**, 2220.
8. Riley, H. D. Jr. (1958): J. Lab. Clin. Med., **52**, 840.
9. Sanford, J. P., Favour, C. B., Mao, F. H. and Harrison, J. H. (1956): Amer. J. Med., **20**, 88.
10. Jackson, G. G., Grieble, H. G. and Knudsen, K. B. (1958): J. Amer. Med. Assoc. **166**, 14.

THE PHYSICAL, INFECTIVE, ALLERGIC, CLIMATIC AND ATMOSPHERIC IONIZATION FACTORS IN THE AETIOLOGY PATTERN OF RESPIRATORY DISEASE*

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The various factors likely to be involved in the initiation and maintenance of acute and chronic respiratory diseases were described and the integration of multiple such factors into an aetiology pattern was described.

In the 'catarrhal' child and even in the older person with frequent 'head colds' or 'chest colds' (bronchitis) infection is generally held to be responsible and many such patients are in consequence submitted to antibiotic therapy. In the majority of the cases, however, the symptoms are a manifestation of an allergic reaction. Aggravation of symptoms is certainly associated with superimposed infection but, if the basic allergic condition is effectively controlled, the liability to, and effects from, infection are significantly diminished. The transition to chronic bronchitis in some of these patients occurs possibly as a result of the aspiration of pathogenic organisms from an associated acute sinusitis leading to lower respiratory-tract infection.

The aetiology of chronic bronchitis in persons of middle age and older is not clearly defined. This condition is probably not primarily of infective origin nor resulting from repeated infections as commonly thought. The characteristic feature is the production of excessive sputum due to a disturbance of mucus secretion in the bronchi. The responsible agent for this disturbance has still to be confirmed. The possibilities of an allergic basis for the condition were considered and investigations suggested in pursuance of this view. The influence of climate in chronic bronchitis was discussed in relation to environmental conditions such as industrial city life, the inhalation of dust and fumes, smog, and also cigarette smoking. The possible allergic basis in silicosis was considered and reference made to the work of the Pneumoconiosis Research Unit in this connection.

The relation of climate to allergic respiratory diseases in South Africa and elsewhere was described with emphasis on the 'climate group' of sufferers whose symptoms were aggravated and indeed often initiated at the coast. The greater allergenicity of the house dust at the coast appeared to be the responsible factor. The possible reasons for the difference in potency in inland and coastal house dusts were presented.

Reference was made to views on the influence of atmospheric ionization on the animal body at the cellular level as well as to its effects on the health of man in general and on allergic respiratory conditions in particular.

* Summary of paper presented at a Staff Scientific Meeting, South African Institute for Medical Research, Johannesburg, 22 February 1960.

VAN DIE REDAKSIE : EDITORIAL

MIDDELS TEEN BAKTERIEË EN ANTIBIOTIESE MIDDELS

Daar verskyn al meer verslae in die mediese literatuur oor die toenemende voorkoms van infeksie met stafilokokke en oor die moeilikhede wat gepaard gaan met die behandeling van hierdie soort infeksie. Voor die ontstaan van antibiotiese middels was die stafilokokke, wat gegroepeer is in patogene en nie-patogene soorte, nog maar altyd vir die meeste praktisyns alomteenwoordig en verantwoordelik vir bloedvinte, huidinfeksies en gewone infeksies van wonde. Sedert die ontwikkeling en die algemene gebruik van antibiotiese middels het sekere soorte stafilokokke 'n weerstand ontwikkel teen die meer algemene soorte van hierdie middels. Daar is dus vandag 'n groot gedeelte van die hospitaalinfeksies wat waarskynlik veroorsaak word deur die sogenaamde ‚hospitaal'-stafilokokke. Hierdie stafilokokke, wat deur spesiale metodes van tipering geklassifiseer kan word as faag 80 - 81, het 'n sterk weerstand teen behandeling met die meeste soorte antibiotiese middels wat in die algemene gebruik is.

Of hierdie kiemsoorte met weerstand teen antibiotiese middels ontwikkel het van ‚wilde' stafilokokke deur ongenoegsame terapeutiese dosisse, wat sommige kieme doodgemaak het en ander toegelaat het om te herstel, en of die normale genoemde stafilokokke-bevolking van 'n wond waarin infeksie is, gesuiwer is van sy ‚wilde' bestandele deur differensiële uitwissing met antibiotiese middels, maak vir die doel van ons huidige skrywe nie saak nie. Hospitale en verpleeginrigtings oral oor die wêreld is vol van ‚hospitaal'-stafilokokke en baie perfekte en suksesvolle operasies word geruïneer of benadeel deur vertraagde genesing as gevolg van hierdie soort infeksie.

'n Bietjie van daardie ‚terugsig' waarvoor baie mediese en natuurwetenskaplike teoretici bekend staan, mag ons help om hierdie probleem beter te verstaan. Alhoewel die bakteriologie as 'n wetenskap nog nie honderd jaar oud is nie, het bakterieë tog al bestaan sedert die vroegste eeue, en dit moet dus die geval wees dat 'n proses van natuurlike seleksie ook op die bakterieë van toepassing was deur al hierdie tydvakke. Die uitwerking van antibiotiese middels, wat maar slegs 'n paar jaar tevore ontdek is, is een van die maniere waarop die natuur die bakterieë in bedwang hou. As dit nie hiervoor was nie sou bakterieë die wêreld al lankal oorstroom het. Die proses van natuurlike seleksie was waarskynlik ook aktief ten opsigte van die lewende organismes waaruit antibiotiese middels ontstaan. Bakterieë wat nie in staat was om weerstand te bied teen antibiotiese middels nie, sou sonder twyfel lankal uitgewis gewees het. Die oorblywendes wat ons vandag kry moet dus beskou word as 'n geselekteerde groep met die latente vermoë tot weerstand teen antibiotiese middels, en ons kon dit verwag het dat soorte met weerstand gou te voorskyn sou tree sodra hulle in aanraking kom met ons antibiotiese terapie.

Dit wil dus voorkom asof die bloeitydperk van antibiotiese terapie binnekort tot 'n einde moet kom. Ander en meer doeltreffende middels sal seker wel ontdek word, maar die proses van natuurlike seleksie en aanpassing sal ook weer help om die bakterieë bestand te maak teen hierdie nuwe aanslae, sodat dit die meeste is wat ons kan verwag om 'n nuwe groep bakterieë aan te tref met weerstand teen die nuwere antibiotiese middels.

Waarin is die oplossing dan geleë? Ons dink onvermydelik aan chemoterapie. Sintetiese chemikalieë is somtyds heeltemal nuut wat betref die lewe van bakterieë. Voor die jare rondom 1920 het geen gonokokkus of pneumokokkus, byvoorbeeld, ooit 'n sulfonamied teengekom nie, en daar kan dus nie 'n weerstand wat ter eniger tyd gereed is teen die nuwe bedreiging, wees nie. Dat 'n sekere mate van weerstand soms ontwikkel word, is 'n voorbeeld van 'n fundamentele beskermende beginsel in die natuur.

Op p. 537 van hierdie uitgawe plaas ons 'n voorlopige verslag oor die behandeling van absesse van die bors met 'n nuwe chemiese teenmiddel teen bakterieë (furaltadone). Die resultate is bemoedigend en 'n meer omvangryke toets van hierdie nuwe middel is waarskynlik aangewese.

ANTIBACTERIAL DRUGS AND ANTIBIOTICS

More and more reports are appearing in the medical literature about the increasing incidence of infection with the 'hospital' staphylococcus and about the difficulties associated with the treatment of these infections. Before the development of antibiotics, staphylococci, while grouped into pathogenic and non-pathogenic varieties, were still, to most practitioners, the ubiquitous frequenters and causal agents of boils, skin infections, and common wound infections. Since antibiotics have been developed and their use become general, certain staphylococci were found to have become resistant to the action of the commoner antibiotics, until today a fair proportion of hospital infections can be ascribed to the 'hospital' staphylococcus, which can, by special typing, be classified as phage 80 - 81, and which strongly resists treatment with most of the antibiotics commonly in use.

Whether these antibiotic-resistant strains have been developed from 'wild' staphylococci by inadequate therapeutic doses which, having failed to kill all, have allowed the survivors to recover from the near-mortal attack, or whether the normally mixed staphylococcal population of an infected wound has been purified of its 'wild' components by differential killing-off with the antibiotic is, for our present purpose, immaterial. Hospitals and maternity homes all over the world swarm with the 'hospital' staphylococci, and many perfect and otherwise successful operations are marred or ruined by delayed healing resulting from this infection.

A little of the 'hindsight' for which medical and other scientific theoreticians are rightly famous may lead us to understand this problem better. Although bacteriology as a science is not 100 years old, bacteria have existed on earth from the remotest ages and natural selection has doubtless been operating on them for all these aeons. Antibiotic action, discovered only a few years ago, is one of the many ways

in which Nature has kept the bacteria in check, and but for which they would have overrun the earth. Natural selection has also doubtless been operating on the living organisms which produce antibiotic substances. The bacterium which was unable to withstand antibiotics or to develop a resistance to them would doubtless have become extinct ages ago. The survivors which we know today are therefore to be regarded as a select group with latent powers of resistance to antibiotics, and we could have anticipated that resistant strains would quickly come to light when they encountered our antibiotic therapy.

It would appear therefore that the honeymoon of antibiotic therapy may shortly be ending. Doubtless other and more efficient antibiotics will be discovered, but just as certainly natural selection or adaptation will help the bacteria to resist these new onslaughts, so that all we can anticipate is a rash of new bacteria resistant to the newer antibiotics.

Where then does the solution lie? Inevitably one turns to chemotherapy. Synthetic chemicals are something new in bacterial experience; before the 1920s no gonococcus or pneumococcus had ever encountered a sulphonamide and there could not possibly be any built-in, quickly-summoned resistance to the new challenge. That a certain amount of resistance is sometimes developed is an example of Nature's more fundamental powers for preserving the species.

In this issue (p. 537) will be found a preliminary report on the treatment of breast abscess with a new chemical antibacterial agent (furaltadone). The results are encouraging and a wider trial of the new agent (one of the nitrofuran group) would appear to be justified.

ACYANOTIC FALLOT'S TETRALOGY : A CLINICAL REPORT OF SIX CASES*

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The clinical picture in Fallot's tetralogy ranges from the very severe form with marked pulmonary stenosis and significant right-to-left shunt, on the one hand, to the form with mild pulmonic stenosis and primarily a left-to-right shunt, on the other (Fig. 1). The above varieties have 3 fundamental features in common, viz. pulmonic stenosis (either infundibular or valvular or both), high ventricular septal defect, and equalization of systolic pressures in both right and left ventricles. All patients with Fallot's tetrad, severe and mild, are liable to have increased infundibular 'narrowing' with resultant blue or unconscious spells. The other aspects of Fallot's tetralogy—dextro-position of the aorta, right ventricular hypertrophy, and overriding of the ventricular septal defect by the aorta—are neither clinically nor haemodynamically important. This paper describes 6 patients with Fallot's tetralogy who were not cyanosed clinically, but who belonged haemodynamically to the tetrad group. The hazards of cardiac catheterization in patients with Fallot's tetralogy are confirmed.[1] One patient developed a syncopal spell during the investigation, and remained unconscious for 2½ hours.[2]

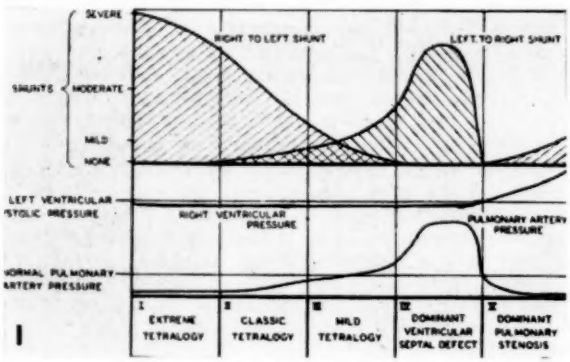

Fig. 1. The 'spectrum' of ventricular septal defect and pulmonary stenosis (modified from McCord *et al.*[11]) Groups I, II and III are tetralogies. Group IV may or may not be tetralogy.

* Paper presented at the 42nd South African Medical Congress (M.A.S.A.), East London, C.P., September - October 1959.

Methods

All the patients were examined clinically by at least 2 of the authors. A 12-lead electrocardiogram, full radiological survey, and phonocardiogram (Sanborn twin-beam), were performed in each case. In 5 cases cardiac catheterization was carried out under mild general anaesthesia with sodium thiopentone (pentothal) after premedication with meperidine hydrochloride (pethedine), nalorphine hydrochloride (lethidrone), prochlorperazine maleate (stemetil) and promethazine hydrochloride (phenergan). The 6th patient was catheterized under local anaesthesia.

The oxygen content of the blood was measured by the Van Slyke technique and the oxygen saturation by cuvette oximetry (Waters-Connoly oximeter). Pressures were recorded on a direct-writing recorder through a Sanborn capacitance electromanometer.

CLINICAL FEATURES

Symptoms

The clinical features are summarized in Tables I and II.

TABLE I. SYMPTOMS

Case No.	*Age*	*Sex*	*Dyspnoea*	*Cyanosis at rest*	*Cyanosis on crying*	*Cyanosis on exertion*	*Sweating*	*Failure to thrive*	*Respiratory infections*	*Squatting*	*Syncope*	*Angina*
1	4	M	+	—	+	+	—	+	+	—	—	—
2	2½	F	+++	—	+	+	—	—	—	—	once	—
3	4½	M	++	—	—	—	—	—	—	—	—	+
4	4½	M	+	—	—	+	+	+	++	+	once	—
5	5	F	+	—	—	—	—	—	—	—	—	—
6	17	M	+	—	—	—	—	—	—	—	—	—

+ = mild. ++ = moderate. +++ = marked.

There were 4 boys and 2 girls. Their ages ranged from 2¼ years to 17 years. Shortness of breath on exertion was present in every case and every patient was more incapacitated in hot weather. Cyanosis at rest was absent in every patient, but cases 1 and 2 became cyanosed during crying and exertion. Case 4 occasionally showed cyanosis on exertion. Squatting was noted in case 4. Syncopal attacks occurred on only one occasion in each of 2 cases. Failure to thrive was a presenting symptom in 2 patients. Frequent upper-respiratory-tract infections were present in 2 patients. Excessive sweating was a feature in one boy and chest pain on effort in another boy.

Signs

All except case 1 were well developed and well nourished. A plethoric appearance was noted in all, but no definite cyanosis or clubbing. The finger tips were abnormally red in 5 out of the 6 cases. Blood-pressure readings were normal. A slightly collapsing pulse was noted in case 4. Cardiomegaly was not a feature and the heart action was quiet in all but one case. A right ventricular parasternal heave was palpated in all patients, while cases 3 and 6 had an apical left ventricular heave as well. Pulmonary systolic thrills were present in all and in case 4 a systolic thrill was present in the epigastrium as well. A systolic thrust in the pulmonary area was recorded in 3 patients and a diastolic shock in the same region in 2 patients. The first heart sound was normal in 5 patients and accentuated in 1 patient. The second heart sound was split in 5 patients; in 4 patients the 2nd component (pulmonary) was softer than the 1st, and in 1 patient they were equal; in case 4 the second heart sound was recorded as single. Ejection pulmonary systolic murmurs of grade 3 - 4 were present in all patients.

A rough early diastolic murmur replacing the 2nd component of the second heart sound was audible in case 4. This was found at open-heart surgery to be due to incompetence through a rudimentary, abnormally situated, extracardiac pulmonary valve. A rumbling apical mid-diastolic flow murmur (which disappeared after corrective surgery) was noted in case 3. There was no evidence of congestive cardiac failure, elevated jugular venous pressure, hepatomegaly, or peri-orbital oedema, in this series.

The electrocardiograms were abnormal in all cases. Right ventricular hypertrophy was present in every one.[3,4] The pattern, however, varied. A tall, notched, R pattern in VI was recorded in 3 cases—the voltage being 11 mm., 24 mm. and 26 mm. respectively (Fig. 2, case P.R.). An rsR′ configuration with a delayed onset of intrinsicoid deflection (0·04 second) was seen in one patient (Fig. 2, case J.R.). Two further patients had prominent S waves in lead 1 and tall R waves in lead 3—their axis deviation measuring +105° and +85° respectively. They also showed upright T waves in VI, reported as right ventricular hypertrophy in the first year of life by Ziegler[5] (Fig. 2, case C.J.). We have not seen this latter pattern in normal children under the age of 10 years and have regarded it as a sign of right ventricular hypertrophy in this particular age group. Only one patient showed left ventricular hypertrophy in addition to his right ventricular hypertrophy (Fig. 2, case C.J.). Abnormal P waves were not seen in this series.

Phonocardiography showed classical pulmonary ejection systolic murmurs in all cases. The systolic murmur occupied the whole of systole (Fig. 3). The second heart sound was split in 5 patients, the second pulmonary portion being softer than the aortic element. The splitting was moderately wide, being 0·06 - 0·08 seconds. In case 4 the second sound appeared to be single. A pulmonary incompetence murmur replacing the 2nd component of the second sound was recorded in this case. An apical mid-diastolic murmur was recorded in 1 case (Fig. 3). Amyl nitrite was administered to 2 patients.[6] In one of them (case 6) the systolic murmur practically disappeared (Fig. 4), whereas in the other (case 4), while the

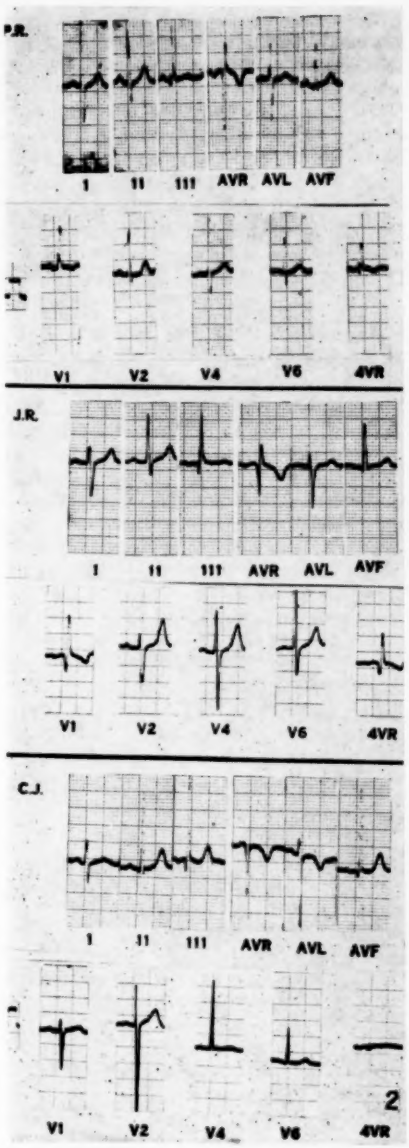

Fig. 2. Electrocardiographic patterns.

TABLE II. SIGNS

Case No.	Pleth.	Red fingers	Club-bing	BP mm. Hg	Cardio-megaly	Quiet heart	LVH	RVH	Syst. thrill	MI	P2	SM	MDM	EDM	CCF
1	+	+	? early	75/40	–	+	–	+	Pulm. area	Normal	Split, compo-nents equal	Gr. 4	–	–	–
2	+	+	–	90/50	–	+	–	+	Pulm. area	Normal	Split, 2nd com-ponent soft	ejec-tion Gr. 4	–	–	–
3	+	+	–	90/60	–	+	+	+	Pulm. area	Normal	Split, 2nd com-ponent soft	Gr. 4	Gr. 2 at apex	–	–
4	+	+		110/70	–	+	–	+	Epigas-trium Pulm. area	Normal	Single	Gr. 5	–	Gr. 2 harsh at Pulm. area	–
5	+	+	–	90/65	+	–	–	+	Pulm. area	Normal	Split, 2nd com-ponent soft	Gr. 4	–	–	–
6	+	–	–	110/70	+	+	+	++	Pulm. area	Accen-tuated	Split, 2nd com-ponent soft	Gr. 6	–	–	–

Pleth = Plethoric appearance. LVH = Left ventricular enlargement. RVH = Right ventricular enlargement. M1 = First heart sound at apex. P2 = Second heart sound at pulmonic area. SM = Systolic murmur. MDM = Mid-diastolic murmur. EDM = Early diastolic murmur. CCF = Congestive cardiac failure.

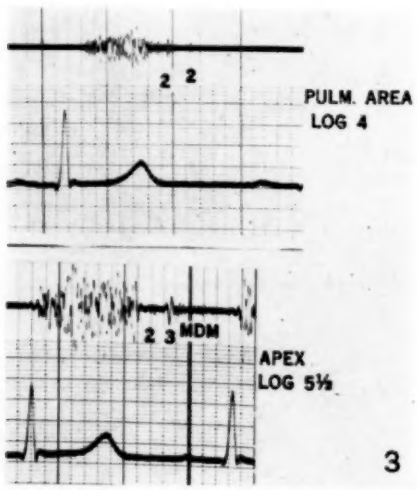

Fig. 3. Phonocardiogram showing ejection systolic murmur, wide splitting of 2nd sound with soft second component, and mitral flow murmur.

TABLE III. X-RAY FEATURES

Case No.	CTR	PAS	PV	RA	LA	RV	LV	Aorta
1	50%	N	±	N	+(DD)	+	+	High Prom.
2	58%	N	N	±	N	+	N	Prom.
3	51%	+	+	+	+(DD)	+	+	N
4	50%	N	+	+	N	+	N	N
5	50%	N	+	N	+(LAA)	+	N	N
6	50%	+	+	+	N	+	+	High Prom.

CTR = Cardiothoracic ratio. PAS = Pulmonary artery segment. PV = Pulmonary vasculature. RA = Right atrium. LA = Left atrium. RV = Right ventricle. LV = Left ventricle. DD = Double density. LAA = Left atrial appendage. N = Normal. + = Enlarged or increased. ± = Doubtfully enlarged. Prom. = Prominent.

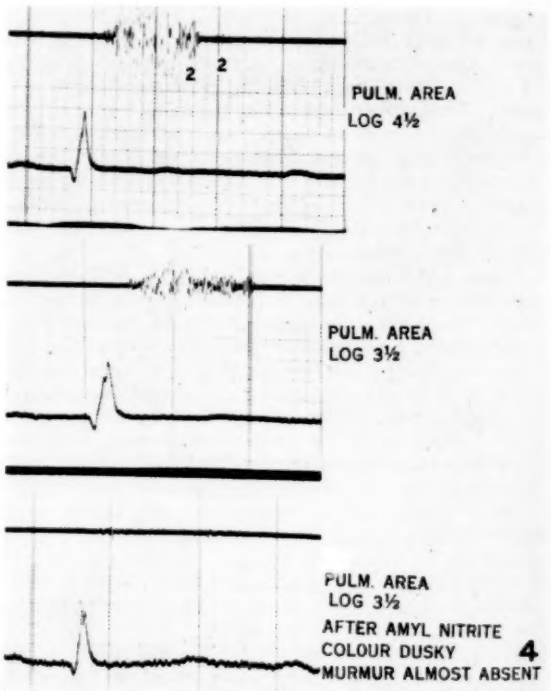

Fig. 4. Phonocardiogram showing marked diminution of ejection systolic murmur after inhalation of amyl nitrite.

pulmonary incompetence murmur disappeared, the systolic murmur became louder in early systole (Fig. 5).

X-Ray features are summarized in Table III. The cardiothoracic ratio was 50% in 4 patients, 51% in 1 case and 58% in 1 case. The pulmonary artery segment was prominent in 2 cases. The lung vasculature was increased in 4 patients, doubtfully increased in 1 and normal in 1. Right atrial enlargement was noted in 4 patients and left atrial enlargement in 3. The right ventricle was enlarged in all 6 and the

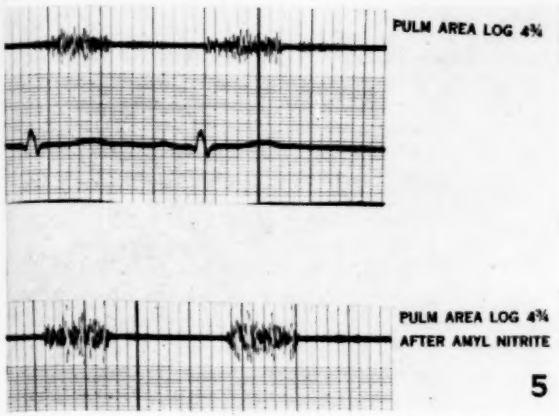

Fig. 5. Phonocardiogram showing increased intensity of early vibrations of systolic murmur after amyl nitrite.

left in 3 patients. The aortic arch was prominent in 3, and left-sided in all (Figs. 6 and 7).

Haemodynamic data are tabulated in Table IV. Cardiac catheterization showed equalization or near equalization of systolic pressures in the right ventricle and systemic artery in all cases. The brachial artery saturation was normal in case 3 (97%) and case 6 (90%) at the altitude of 6,000 feet, and 88% in case 5. Unfortunately the study in case 2 was completed during a syncopal attack. In cases 1 and 4 the patients developed mild clinical cyanosis during the procedure and hence their brachial artery saturations were decreased to 85% and 82% respectively. A pulmonary systolic gradient was demonstrated in all cases, being at valvular level in 2 cases, at infundibular level in 3 cases, and valvular and infundibular in 1 case. The pulmonary-artery pressure was elevated, despite the presence of pulmonary stenosis, in 4 patients, and in one of these the pulmonary-artery pressure was 25/5 mm. Hg despite its recording during an unconscious spell. The mean right atrial pressure was elevated in 3 cases and normal in 3. 'Pulmonary capillary pressure' was elevated in 1 of 3 patients where a satisfactory wedge tracing could be obtained.

Significant left-to-right shunts were present in 5 cases and possibly in the 6th (case 2), where a pulmonary artery sample measured 70·5% oxygen saturation before the syncopal spell and 41% during the spell. Right-to-left shunts were present in 4 cases during catheterization.

DISCUSSION

In 1954 Wood *et al.*[7] noted that in a series of 80 cases of tetralogy 10 patients were acyanotic at rest. The clinical features were similar to those of Roger's disease. However, effort tolerance was reduced in all cases and 4 squatted when breathless. The heart was quiet in its action and the jugular venous pressure was not raised. The pulmonary second sound was single in all cases but one. The electrocardiogram was normal in 3. At cardiac catheterization the right ventricular systolic pressure equalled that in the brachial artery or aorta. The pulmonary-artery pressure was normal in 3 and low in the remainder. The shunting of blood was negligible in 3, bidirectional in 1, with slight right-to-left shunting in 5 and slight left-to-right in 1.

Rowe *et al.*[8] described 4 infants with the clinical features of ventricular septal defect in whom further studies suggested a diagnosis of tetralogy of Fallot. The main symptoms were failure to thrive and frequent lower-respiratory-tract infections. All had systolic murmurs localized to the lower left

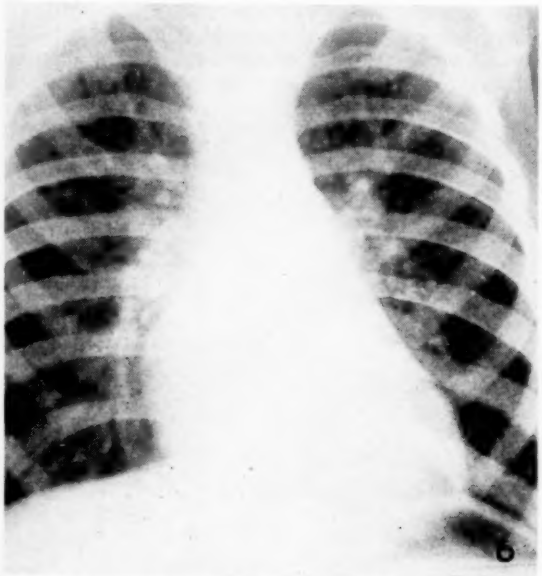

Fig. 6. Radiograph showing right and left ventricular enlargement, prominent pulmonary artery and prominent lung vascularity.

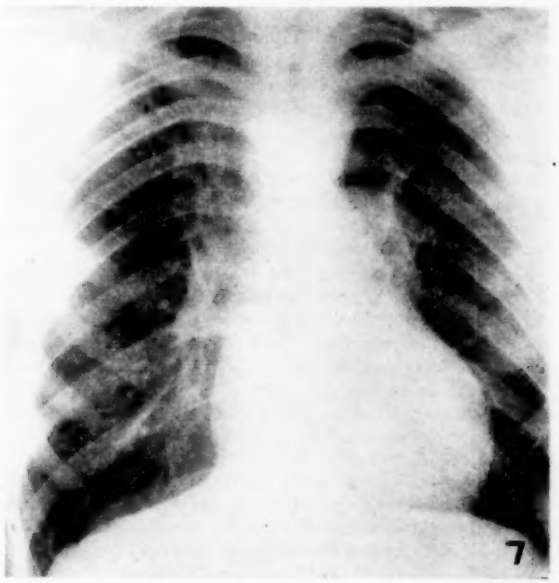

Fig. 7. Radiograph showing right ventricular enlargement, prominent pulmonary arteries and high aortic arch.

TABLE IV. HAEMODYNAMIC DATA

Case No.	Pressure (mm. Hg.)						Oxygen saturation (vols.%)				Flow (litres/square metre/minute)			
	WPA	Pulm. Art.	RV Outflow	RV Inflow	Brach. Art.	Rt. Atrium	SVC	RV	Pulm. Art.	Brach. Art.	Systemic	Pulm. Art.	L—R Shunt	R—L Shunt
1	8/4	44/24	75/0	75/0	75/45	m=2	10·27	10·27	11·29	13·6 (85%)	4·6	6·6	2·0	1·3
2	—	25/2	28/2	88/2	85/40	m=6			*11·25 †6·4	†7·1 (52·5%)	—	—	—	—
3	—	45/25	45/3	90/8	90/70	m=5	11·76	13·8	13·8	16·57 (97%)	2·66	5·0	2·34	Nil
4	m=15	34/20	80/5	80/5	80/50	13/8 m=10	12	15/2	14	16·2 (82%)	5·1	9·7	4·6	0·68
5	—	38/33	38/15	85/12	85/63	15/9 m=13	12·28	12·4	13·8	16·62 (88%)	4·4	6·6	2·2	0·76
6	15/5 m=8	30/5	50/0	100/0	100/65	m=3	12·2	14·4	14·4	16·2 (90%)	4	5·8	1·8	Nil

WPA = Wedged pulmonary artery. Pulm. Art. = Pulmonary artery. RV = Right ventricle. Brach. Art. = Brachial artery. Rt. = Right. SVS = Superior vena cava. L—R = Left to right. R—L = Right to left. m = Mean pressure (electronically integrated). *Specimen obtained before the development of a syncopal spell. † Specimen obtained during a syncopal spell.

sternal border. The pulmonary second sound was split in 2 cases. X-ray showed slight to moderate cardiomegaly and pulmonary plethora in all and a right aortic arch in 1. The ECG showed a normal axis in 2 and combined ventricular hypertrophy in all. Cardiac catheterization showed systemic systolic presures in the right ventricle and large left-to-right shunts. In one case pulmonary incompetence was present during life and autopsy showed a rudimentary pulmonary valve.

Bashour and Winchell[9] described 3 cases of Fallot's tetralogy with a preponderant left-to-right shunt at rest. They noted that the shunt sometimes reversed with exercise.

Calazel *et al.*[10] described abnormally well developed pulmonary vascularization in certain cases of Fallot's tetralogy. They suggested that in some tetrads the ventricular septal defect was more important than the pulmonary stenosis.

In 1957 McCord *et al.*[11] described 5 varieties of Fallot's tetralogy. Type 3—the mild tetrad—was characterized by the absence of cyanosis and minimal symptoms. In this, 7 patients were included, but in 3 the left ventricular systolic pressure exceeded that of the right ventricle. This latter group should not, by definition, be included in a group of tetrads. The clinical findings, radiological features and ECG tracings were similar to those described previously.

The cases in the present series are similar to those described in the literature. The pulmonary stenosis is moderate in all cases, the pulmonary-artery pressure being normal or elevated in the majority. The left-to-right shunt at the ventricular level predominates, and in some cases a small right-to-left shunt may be present. The separation of this type of tetralogy from the 'low' ventricular septal defect with moderate pulmonic stenosis and left-to-right shunt may be impossible if the systolic pressure in the aorta or systemic artery is equal to the right ventricular systolic pressure. Clinically, however, the tetrad variety has either a single pulmonary second sound or, more frequently, splitting of the second sound with either a decrease in intensity of the pulmonary component or both pulmonary and aortic elements equal in intensity.

The patients with ventricular septal defect and pulmonary stenosis usually show a split second sound with both components equal. Squatting and syncopal attacks probably only occur in the tetrad variety. The production of cyanotic attacks with a decrease in pulmonary systolic murmur and some decrease in pulmonary-artery pressure during cardiac catheterization occurs, as far as we know, only in the tetralogy variety. In one of our cases an unconscious or syncopal spell with complete absence of the pulmonary systolic murmur, lasting 2½ hours, was induced by cardiac catheterization.[2] A striking decrease in intensity of the systolic murmur after inhalation of amyl nitrite is typical of tetrads[6] (Fig. 4). However, this finding is not, in our experience, invariable and case 4, in whom a tetralogy was proved at operation, showed an increase in intensity of the murmur on several occasions after inhaling amyl nitrite (Fig. 5).

The acyanotic variety of Fallot's is a definite entity. Its clinical features, X-ray findings, ECG abnormalities, and haemodynamic findings, have been detailed. The absence of cyanosis, in spite of an 'overriding' aorta, is dependent in

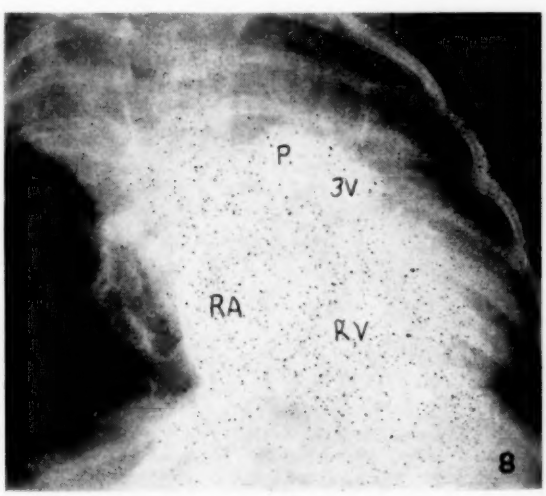

Fig. 8. Angiocardiogram showing infundibular stenosis, but no filling of the 'overriding' aorta (3V = infundibular chamber).

these cases on the severity of the pulmonary stenosis. If the resistance offered by the pulmonary outflow tract, or valve, is lower than systemic resistance, blood will shunt left-to-right only. We have recently seen an infant aged 8 months who is not cyanosed at rest but has frequent cyanotic and syncopal attacks. Cardiac catheterization revealed infundibular stenosis, ventricular septal defect with left-to-right shunt, and equalization of the right ventricular and systemic blood pressure. Angiocardiography demonstrated an infundibular chamber and large pulmonary arteries. The aorta did not fill simultaneously with the pulmonary artery (Fig. 8 and 9) despite its 'overriding' the ventricular septal defect. After

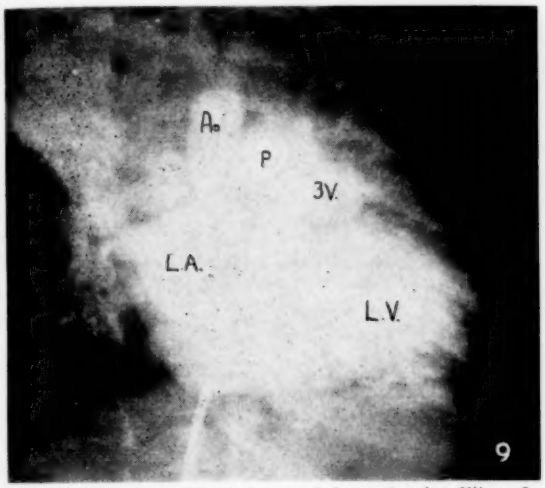

Fig. 9. Same case as Fig. 8, 3 seconds later, showing filling of aorta from left ventricle.

the anaesthetic was terminated the baby developed a severe 'blue spell', which persisted for about 4 hours.

We have previously shown[1,2] that the degree of obstruction to pulmonary flow may increase spontaneously and strikingly after cardiac catheterization. It is believed that this situation, with the production of cyanotic or unconscious spells, may make this disease dangerous. Furthermore, these patients are all symptomatic. Patients with spells rarely reach adulthood. It is felt, therefore, that the prognosis is poor, and, with the progress of open-heart surgery, we believe that corrective surgery should be advised in all cases. To date 4 of our patients have undergone corrective surgery and there has been 1 death amongst them.

SUMMARY

1. The significant components of the acyanotic variety of Fallot's tetrad are described. They comprise equalization of systolic pressures in both right and left ventricles, a ventricular septal defect, and moderate pulmonic stenosis.

2. All cases have dyspnoea on exertion with loud systolic murmurs in the pulmonary area or lower left sternal border. The pulmonary second sound is usually split, with decreased intensity of the pulmonary component. In some cases it is single.

3. The ECG shows right ventricular hypertrophy and may show left ventricular hypertrophy as well.

4. X-ray examination shows normal or slight cardiomegaly, with normal or increased pulmonary vasculature. A right aortic arch has been reported in the literature in only 1 instance and was not seen in our series.

5. Cardiac catheterization studies reveal equalization of right ventricle and aortic pressures. A left-to-right shunt is demonstrated in the majority of cases. Systemic arterial saturation is usually normal except during cyanotic or unconscious spells. Cardiac catheterization has induced cyanotic and unconscious spells.

6. The possibility exists of sudden death following on unconscious spells despite the presence of a left-to-right shunt at ventricular level. Corrective surgery is recommended.

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REFERENCES

1. Braudo, J. L. and Zion, M. M. (1960): Amer. Heart J., **59**, 10.
2. *Idem* (1959): Brit. Med. J., **1**, 1323.
3. Nadas, A. S. (1957): *Paediatric Cardiology*. Philadelphia and London: W. B. Saunders.
4. Hollman, A. (1958): Brit. Heart J., **20**, 129.
5. Ziegler, R. F. (1956): Amer. Heart J., **52**, 533.
6. Vogelpoel, L., Schrire, V., Nellen, M. and Swanepoel, A. (1959): Amer. Heart J., **57**, 803.
7. Wood, P., Magidson, O. and Wilson, P. A. O. (1954): Brit. Heart J., **16**, 387.
8. Rowe, R. D., Vlad, P. and Keith, J. D. (1955): Circulation, **12**, 230.
9. Bashour, F. and Winchell, P. (1955): Ann. Intern. Med., **42**, 1227.
10. Calazel, P. *et al.* (1956): Arch. Mal. Cœur, **49**, 206.
11. McCord, M. C., Van Elk, J. and Blount, S. G. Jr. (1957): Circulation, **16**, 736.

A CASE OF KLINEFELTER'S SYNDROME COMPLICATED BY DIABETES AND DIABETIC GLOMERULOSCLEROSIS

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Klinefelter's syndrome was first described in 1942.[1] Heller and Nelson[2] pointed out that there were 3 consistent features of the syndrome, namely small testes, azoospermia and high urinary gonadotrophin, while the other features described, including gynaecomastia, were variable. In 1958 Ferguson-Smith[3] found that only sterility and small testes were constant features and suggested the name primary micro-orchidism for the syndrome.

Although the syndrome is being more often diagnosed, to the best of our knowledge no other case of primary micro-orchidism complicated by diabetes mellitus and ultimately diabetic glomerulosclerosis has been described. It is felt that in this case the course of the diabetes was influenced by the hypogonadism. Moreover, the patient was given testosterone by implant as substitution therapy for his

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hypogonadism, as was suggested by Heller and Nelson.[4] This therapy appears to have had an unfavourable effect on the progress of the diabetes.

CASE REPORT

The patient, a European male, then aged 51 years, was first admitted to the Johannesburg General Hospital on 23 November 1955 in diabetic ketosis. He was a deaf-mute and the details of his past history were obtained from his wife and his brother. As far as is known, his mother had a normal pregnancy and he was a healthy full-term baby. At the age of 6 months he had a pyrexial illness accompanied by irritability. He recovered, but at the age of 2 years he was found to be deaf and in due course was sent to a school for the deaf. At no stage was he mentally retarded. Little is known about his puberty, but as an adult he found it necessary to shave only once or twice a week. At the age of 25 years he married. According to his wife he was potent but intercourse only took place once every month or two and conception did not occur.

At the age of 40 years he began to lose weight progressively and was found to have diabetes mellitus. He was referred to the Johannesburg General Hospital Diabetic Clinic in 1950 at the age of 46 years. As he lived in a rural area his attendance at the clinic was irregular and in consequence his glycosuria was difficult to control. However, he was never ketotic.

His family consisted of mother, father, 3 brothers and a step-brother. One brother died, perhaps of tuberculosis, at the age of 21 years. The other brothers, all older than the patient, are alive and well and have substantial families. There was no family history of diabetes.

On examination he was seen to be a tall, thin, pale man who looked younger than his stated age. His skin was soft and his axillary and pubic hair was scanty, of fine texture, and of female distribution. His proportions were eunuchoid, with a female distribution of fat. The penis was normal but the testes pre-puberal in size. His body measurements (in inches) were as follows: Height 72½, span 76, vertex-pubis 33½, pubis-heel 39. Blood pressure 110/72 mm. Hg. Heart not enlarged; all the peripheral pulses palpable. Liver palpable 2 fingers below costal margin; smooth and not tender. No oedema. Visual fields normal. No signs of peripheral neuritis.

Laboratory investigations. Blood sugar 400 mg./100 ml., blood urea 36 mg./100 ml., haemoglobin 17·1 g./100 ml., PB iodine 8·3 μg./100 ml. (normal 3·5 - 8·0, usual values 4 - 6). 17-Ketosteroids (as dehydro-iso-androsterone) 6·8 mg./24 hours (normal 7 - 30 mg./24 hours, usual values 10 - 25). Urine: Sugar 4+, acetone present, no albumin, occasional pus cells, growth of coliform bacilli on culture.

The patient was discharged on insulin therapy (30 - 40 units IZS per day) and did not attend at the hospital until his second admission.

Second admission. He was readmitted on 1 March 1957 for control of his diabetes. The fundi now showed micro-aneurysms and hard exudates. There was a loss of sensation over both lower limbs and in the area supplied by L2 - S1. The following additional *laboratory investigations* were carried out: Haemochromatosis was excluded by the serum-iron level (which was normal) and liver biopsy. A testicular biopsy showed small and large islands of Leydig cells and a few hyalinized tubules. A skin biopsy was reported as being chromatin positive. The Robinson-Kepler-Power test was negative. 17-Ketosteroids 16·6 mg./24 hours. FSH 12 - 24 mouse units/24 hours (normal 6 - 48, usual values 6 - 12). Serum albumin 3·8 g./100 ml., globulin 2·8. Traces of albumin in urine. X-ray of the skull showed a normal pituitary fossa.

Third admission. The patient was readmitted on 2 July 1957 in a diabetic coma. He had developed a severe urinary-tract infection which gave rise to a diabetic pneumaturia.[5] The diabetes and the urinary-tract infection were successfully controlled with antibiotics and insulin. 300 mg. of testosterone propionate were implanted subcutaneously before discharge early in August.

Fourth admission. He was re-admitted on 26 August 1957 in hypoglycaemic coma. There was now a notable pallor. Furthermore, the lower extremities were oedematous and there were small areas of gangrene at the tips of the toes. It was noted that he had begun to grow a beard. Blood pressure 162/84 mm. Hg. *Laboratory investigations:* Haemoglobin 10·6 g./100 ml. Serum albumin 3·0 g./100 ml. Urine: Albumin 2+; 17 hydroxycorticosteroids 9·9 mg./24 hours measured as free cortisone (normal 2·9 - 12·0 mg.).

Fifth admission. The patient was readmitted on 1 November 1957 in a state of acute dyspnoea of 3 days' duration. He was found to have the signs of congestive cardiac failure, with marked swelling of the body and legs. The blood pressure was 160/90 mm. Hg and the diabetic retinopathy was more severe. The peripheral neuritis was also more extensive in the legs. The urine contained 4+ albumin. A marked deterioration in the clinical condition was noted since the previous admission. After a transfusion of packed cells he was discharged to a convalescent home. He required constant supervision because his diabetes was now extremely 'brittle' and he continually lapsed into hypo- and hyperglycaemic coma.

TABLE I. COURSE OF CASE

	Date of Admission					
	Nov. 1955	Mar. 1957	Jul. 1957	Aug. 1957	Nov. 1957	Jun. 1958
Blood pressure (mm. Hg)	110/70		150/90	160/85	160/90	190/100-200/110
Retinopathy	nil	+	++	+++	+++	+++
Oedema	nil	nil	nil	++	+++	++++
Albuminuria	nil	nil	+	++	++++	++++
Serum albumin (g./100 ml.)		3·8	—	3·0	—	2·1
Haemoglobin (g./100 ml.)	17·1	17·0	—	10·6	10·0	10·0
Treatment	Insulin	Insulin	Insulin. Antibiotics	Insulin. Testosterone implant	Insulin. Packed cells	Insulin

Final admission on 5 June 1958. On this occasion the patient was admitted with gross generalized oedema and was extremely dyspnoeic. The blood pressure was now 190/100 mm. Hg and this rose to 200/110 in hospital. The serum albumin fell to 2·1 g./100 ml. and the haemoglobin to 10 g./100 ml. At first he responded to treatment but he developed a severe broncho-pneumonia and died on 21 September 1958.

Autopsy Findings

The autopsy was performed 36 hours after death on a White male of eunuchoid proportions. Both pubic and axillary hair was sparse but facial and scalp hair appeared normal. Oedema of the upper and lower extremities. Penis oedematous but normally developed. First toe of right foot showed early gangrene; pressure sore over left heel.

Heart enlarged (435 g.). All valves competent and cusps normal. Mild degree of atheromatosis of coronary arteries. Aorta and large arteries also showed moderate atheroma. Lungs showed bronchopneumonia. Left kidney weighed 245 g. and right kidney 220 g.; both firm and pale, and capsules thickened; large abscess in right renal medulla. Bladder wall trabeculated and showed haemorrhagic cystitis. Testes small and firm; both about the same size (longest axis 1·5 - 2 cm.). Adrenals markedly enlarged. Thyroid pale and nodular. Pituitary macroscopically normal. Pancreas soft but normal in appearance.

Histology

All the tissues were fixed in 10% formalin or formol-saline. Sections were stained with haemotoxylin and eosin and additional stains were used where necessary.

The testes showed the histological features of chromatin-positive primary micro-orchidism. There were large and small aggregations of pleomorphic Leydig cells with pink cytoplasm, large nuclei, and prominent chromatin. These cells contained no glycoprotein (periodic acid Schiff—PAS—negative) but a moderate amount of intracellular fat was demonstrated (oil red 0). The fat was not identified histochemically. With reticulum stains, a fibrillar network of reticulum in the Leydig-cell aggregations was demonstrated.[6] In a few focal areas there were spindle-shaped cells with large trachychromatic nuclei. The tubules were small, coiled, and lined by a single layer of cells on a poorly defined membrana propria. A combined elastic Masson stain[7] failed to demonstrate any increase of the elastic tissue or thickening of the tunica propria. There was no evidence of spermatogenesis in any of the tubules.

The thyroid gland showed the histological features of an adenomatous colloid goitre.

The pituitary gland contained an excessive proportion of acido-

phil cells. No other abnormal change was observed with haemotoxylin and eosin. Cell counts were carried out on sections taken from various levels stained by the PAS technique. Approximately 3,000 cells were counted. The methods used were as follows: Four hairs were fixed to the diaphragm of the ocular lens and cells on the edge of the hair were counted in a random number of fields under oil immersion. A more accurate random sample was obtained by selecting fields by means of the 'random numbers table', the stage scales being used as coordinates. The cells were divided into acidophils, basophils, amphophils, hypertrophic amphophils and chromophobes, according to the morphological criteria outlined by Russfield.[8] The results obtained are shown in Table II and compared with two other cases of micro-orchidism.

TABLE II. PITUITARY CELL TYPES: COMPARISON BETWEEN THE PRESENT CASE AND TWO RELEVANT CASES (AVERAGE NORMAL VALUES IN BRACKETS)

Cell Type	*Present Case*	*Burt* et al.[15]	*Bell* et al.[20]
Basophil	8·3	10·2 (12·2, 1·86)*	34·7 (11·0)
Acidophil	59·3	33·4 (31·7, 1·74)*	23·5 (37·0)
Chromophobe	15·0	37·8 (51·3, 1·58)*	41·8 (52·0)
Amphophil	10·8	17·7 (4·5, 0·58)*	
Hypertrophic amphophil	6·6	0·9 (0·3, 0·03)*	
Stain	PAS	PAS	H & E

The pancreas contained a slight excess of intralobular and interlobular connective tissue, but no comment could be made on the islets or parenchymal tissue owing to post-mortem change.

Kidneys. Necrotizing papillitis was present in the right kidney. In addition, there was bilateral chronic pyelonephritis, the glomeruli showing the capillary hyaline spheres of diabetic glomerulosclerosis and the laminated argyrophylia described by Allen[10] as characteristic of diabetic glomerulosclerosis. The vessels showed moderate hyaline thickening.

The lungs showed the histological features of bronchopneumonia. Pus cultured from the lung yielded an abundant growth of *Staphylococcus aureus*.

Liver. The central veins of the liver were dilated and the sinuses were congested. There were also focal areas of necrosis.

Sex typing. The original ante-mortem slides were reviewed by Dr. Murray Barr,[11] who made the following comment: '(The blood showed) female-type neutrophils with a frequency of 1%. They did not have typical drumsticks. This is a low incidence but is sometimes found with the Klinefelter syndrome where there are typical female nuclei in oral smears and skin biopsy'. He found that the techniques used for fixation and staining of the skin were unsuitable for chromatin study.

DISCUSSION

The clinical presentation of this infertile, eunuchoid, male phenotype with small testes was typical of Klinefelter's syndrome. The histological features of the testes confirmed the clinical diagnosis. Although the genetic sex could not be established satisfactorily, the clumping of the pleomorphic Leydig cells and the presence of 'ghost' tubules without lumina and without any evidence of spermatogenesis were in favour of a female genetic sex.[11,12] However, the recent work of Ford[13] suggests that a person with the Klinefelter type of gonadal dysgenesis cannot be termed a genetic female because of the XXY sex-chromosome composition. Whatever the sex it would not influence the occurrence of diabetes and the fluctuations in its course, which are the main features to be discussed.

The patient was first diagnosed as a diabetic 11 years before his first admission to hospital. Until he was admitted the only sign of diabetes was glycosuria. This had been difficult to control, largely owing to the patient's enforced lack of cooperation. He had never been ketotic and there were no complications at that stage, but 11 years after the proven onset of the disease the clinical picture changed from one of a stable diabetic to one of a labile diabetic who frequently lapsed into coma. It should be noted that at no stage did his insulin requirements increase appreciably. With this change the vascular complications of the disease appeared and developed rapidly over a period of 16 months. The nephropathy in particular had a rapidly progressive course.

The interest of this case lies in the fact that a gonadal dysgenesis of the Klinefelter type was complicated by diabetes and ultimately diabetic glomerulosclerosis. The unusual clinical course of the diabetes can be explained by interpreting the relation of the hypogonadism to the anterior pituitary. This relationship has been noted by Russfield,[14] who showed that hypogonadism may be the initiating factor in pituitary hyperfunction and that the deficiency of one endocrine end-organ may lead to pituitary hyperplasia and even neoplasia. Moreover, Burt *et al.*,[15] who studied the post-mortem findings in an uncomplicated case of Klinefelter's syndrome and who also reviewed 21 other cases of hypogonadism, found a high incidence of adrenal or thyroid hyperplasia in these patients. They concluded that these glands may participate in the 'endocrine imbalance' in this syndrome.

It is therefore possible that the diabetes in this patient was initiated by the anterior pituitary gland which was hyperactive as a result of the hypogonadism. Young[16] produced permanent diabetes in a series of classical experiments by the administration of pituitary extract. More recently, Lazarus and Volk[17] produced permanent diabetes in partially pancreatectomized dogs by administration of growth hormone. The long latent period between the onset of pituitary overactivity and the development of the diabetes has been described by Joslin,[18] who points out that in most cases of acromegaly 15 years elapse before diabetes mellitus manifests itself. Whether or not the diabetes was initiated by the pituitary gland, there is experimental evidence that pituitary activity might be expected to influence the course of the disease.

It is likely that the diabetes was of the insulin-deficient type, and the change from hyperglycaemia to ketosis which took place in the last 3 years of the patient's life may have been induced by an excess of growth hormone. It is well known that growth hormone sometimes produces ketosis where insulin is lacking. This has been amply verified experimentally by Gillman *et al.*[19] in baboons deprived of pancreas and pituitary. Furthermore, the anti-insulin effect of growth hormone was demonstrated by Cori and Cori[20] and has since been confirmed by De Bodo *et al.*[21] and other workers.

There is thus good evidence that pituitary hyperfunction can both initiate diabetes and affect its course. It is therefore possible that it may have played a part in the unusual clinical presentation shown by the present patient. In fact, there was biochemical and post-mortem evidence that mild pituitary hyperfunction was present in this case. The levels of serum protein-bound iodine and follicle-stimulating hormone in the urine were above normal. The post-mortem findings of enlarged adrenal glands and the histological picture of an adenomatous thyroid, while by no means conclusive, tend to support the clinical evidence. The question arises which section of the cellular population of the pituitary is responsible for the hyperfunction. The classical view is that the acidophils produce growth hormone. There

was a marked increase in the percentage (59·3) of acidophils in this case as compared to the normal. The increased proportion of acidophils is in contrast to findings in other cases of hypogonadism such as Klinefelter's syndrome,[15,22] in human castration,[8] and in old age.[23] In all these instances an increase in basophils and/or amphophils only has been observed. The administration of androgens probably accounts to some extent for this acidophil increase, because androgens cause granulation of the amphophils and increase the well granulated acidophils.[8] Russfield[8] has suggested that all the trophic hormones of the anterior pituitary are secreted by the amphophil and hypertrophic amphophil series. According to this view the increase in the proportion of these cells which has been found in the present case (10·8% amphophils) suggests pituitary hyperfunction. The cellular changes in the pituitary thus appear to be compatible with an increase of growth hormone.

The testosterone implant appeared to have an unfavourable effect on the diabetes and it is possible that this, too, was related to the function of the pituitary gland. It has been shown experimentally that androgens have an adverse effect on diabetes[24] and this is possibly mediated through the pituitary gland. As pointed out above, androgens may produce a histochemical change in the cells of the pituitary gland and probably this corresponds to a 'shift' in hormone production. Talbot[25] found a drop in 11-oxycorticosteroids in 2 cases of Cushing's syndrome in which testosterone propionate was administered. This shift in hormone production is not a new concept. Russfield[8] has suggested that it may occur in cretins and in gonadal agenesis where there is failure of growth. There is reason to suppose that shifts in hormone production do occur with the administration of exogenous hormones.

The aetiological agent responsible for the vascular complications of diabetes mellitus is not known. ACTH and the adrenal steroids have often been suggested but much doubt has been cast on the role of these steroids as an important factor, both in the development of diabetes[26] and in the vascular complications.[27,28] By contrast, growth hormone has a well established diabetogenic effect.

It is possible that the improvement in retinopathy and nephropathy following ablation of the pituitary gland[29-31] are due to the removal of the source of growth hormone. In our patient the rapid downhill course terminally may well have been associated with a further increase of this hormone.

Although the theory advanced to explain the clinical course in this case conforms with the findings and with certain evidence in the literature it is obviously impossible to be dogmatic. The diabetes mellitus may have run a natural course and perhaps neither the hypogonadal state nor the testosterone implant had any bearing on the disease. However, the observations in this case may be confirmed by future studies in similar cases. It is of interest that Stewart[32] also holds the opinion that there is possibly an increase of growth hormone in this type of gonadal dysgenesis and advances as his evidence the eunuchoid measurements of his cases in the presence of early epiphyseal closure.

SUMMARY

A case of primary micro-orchidism with diabetes mellitus and subsequently diabetic retinopathy and nephropathy is presented. The unusual course of the diabetes is discussed in relation to the finding of pituitary hyperfunction. In addition, comment is made on the possible effect of the administration of testosterone on the development of vascular complications.

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REFERENCES

1. Klinefelter, H. F. jr., Reifenstein, E. C. jr. and Albright, F. (1942): J. Clin. Endocr., **2**, 615.
2. Heller, C. G. and Nelson, W. L. (1945): *Ibid.*, **5**, 1.
3. Ferguson-Smith, M. A. (1958): Lancet, **1**, 928.
4. Heller, C. G. and Nelson, W. O. (1945): J. Clin. Endocr., **5**, 27.
5. Glyn-Thomas, R. and Sandler, A. (1958): S. Afr. Med. J., **32**, 309.
6. De la Balze, F. A., Arrillaga, F. C., Irazu, J. and Mancini, R. E. (1952): J. Clin. Endocr., **12**, 1426.
7. Treurnich, D. (1959): Unpublished data.
8. Russfield, A. B. *In* Mellors, R. C. (1957): *Analytical Pathology*, p. 293. New York: McGraw-Hill.
9. Mellgren, J. (1945): Acta path. microbiol. scand., suppl. 60, 1.
10. Allen, A. C. (1951): *The Kidney*. New York: Grune and Stratton.
11. Barr, M. L. (1958): Personal communication.
12. Ferguson-Smith, M. A., Lennox, B., Mack, W. S. and Stewart, J. S. (1957): Lancet, **2**, 167.
13. Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M. and Shapiro, A. (1959): *Ibid.*, **1**, 709.
14. Russfield, A. B., Reiner, L. and Klaus, H. (1956): Amer. J. Path., **32**, 1055.
15. Burt, A. S., Reiner, L., Cohen, R. B. and Sniffen, R. C. (1954): J. Clin. Endocr., **14**, 719.
16. Young, F. G. (1938): Proc. Roy. Soc. Med., **31**, 1305.
17. Lazarus, S. S. and Volk, B. W. (1959): Arch. Path., **67**, 456.
18. Joslin, E. P. (1959): *The Treatment of Diabetes Mellitus*, 10th ed. London: Henry Kimpton.
19. Gillman, J., Gilbert, C., Epstein, E. and Allan, J. C. (1958): Brit. Med. J., **2**, 1260.
20. Cori, G. T. and Cori, C. F. (1952): J. Biol. Chem., **199**, 661.
21. De Bodo, R. C. and Altszuler, N. (1956): Diabetes, **5**, 194.
22. Beil, H. V. and Golden, A. (1955): Arch. Path., **60**, 117.
23. Pearse, A. G. E. (1953): J. Path. Bact., **65**, 355.
24. Houssay, B. A. (1951): Brit. Med. J., **2**, 505.
25. Talbot, N. B. *et al.* (1947): J. Clin. Endocr., **7**, 331.
26. Ingle, D. J. (1956): Diabetes, **5**, 187.
27. Jakobson, T. (1958): Acta endocr., suppl. 41, 1.
28. Mortimore, G. E., Diraimondo, V. S. and Forsham, P. H. Cited by Thomson, R. H. S. and King, E. L. (1957): *Biochemical Disorders in Human Disease*, p. 536. London: Churchill.
29. Hernberg, C. A., af Björkesten, G. and Vannas, S. (1959): Acta endocr., **31**, 241.
30. Kinsell, L. W., Lawrence, L., Balch, H. E. and Weyand, R. D. (1954): Diabetes, **3**, 358.
31. Luft, R., Oliverona, H., Sjorgrens, B., Ikkos, D. and Llunggren, H. (1955): In *Ciba Foundation Colloquia on Endocrinology*, vol. 8, p. 438. London: Churchill.
32. Stewart, J. S. S. (1959): Lancet, **1**, 1176.

THE CHANGING FACE OF ANAESTHESIA*

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From time immemorial man has sought to attain relief from the pain of surgical operations, but the ideal was only finally attained little more than a century ago, when anaesthesia for surgical procedures was achieved.

In no other branch of medicine during the last quarter of a century has the advance been so rapid and have concepts so often been changed as in anaesthetics. The result of this fluid state is that those caught in it, are strongly tempted to grasp at dogma as a means of establishing routine and stability. There is, for example, the doctor who states that he never uses ether at all; and then there is the one who declares that ether is still the only anaesthetic agent of any value; both of course are completely misguided. It is only by avoiding dogmatism and developing

* Valedictory Presidential Address, Pretoria, 9 February 1960.

an understanding of the complex processes attendant upon the state of anaesthesia that one can hope to achieve success in the practice of this branch of medicine.

As we all know, Long and Morton, in America in 1842, were the first to put ether to practical use as an anaesthetic agent. In 1844, Horace Wells, a dentist also in America, used nitrous oxide for dental extractions. After these two agents had been used for a few years, Simpson, in Scotland in 1847, used chloroform as an anaesthetic.

All these agents were administered by the open method, and it was not until 1862 that Skinner introduced the domett-covered wire-framed mask, which was frequently copied and was later named after one of the imitators—Schimmelbusch, of Berlin. The Skinner or Schimmelbusch mask is still today an indispensable piece of apparatus to the doctor who practises in the country, away from easily accessible hospital facilities.

The popularity of chloroform after it was introduced by Simpson caused ether to be abandoned for a time, and then followed the first major change in the administration technique of anaesthetics. Some fatalities occurred with chloroform and Snow, who incidentally was the first whole-time anaesthetist, constructed an apparatus to deliver a percentage flow of chloroform with oxygen or air. Clover, in 1862, improved on this chloroform apparatus, but he was convinced that ether was safer than chloroform and, after experimenting and improving still further, he produced the Clover's apparatus, which is still remembered by a few of us of the older school.

An apparatus was later constructed in America by Colton for the administration of nitrous oxide, mainly for dental cases, and in 1887 Hewitt, in England, designed the first practical machine for administering gas.

So, by the end of the 19th century, inhalational anaesthesia was firmly established. Needless to say, the surgeons were now getting bolder, and the scope of surgical undertakings grew.

After various attempts at rectal administration of ether had been abandoned, Gwathmay, in 1913, introduced the method of administering a mixture of oil and ether by the rectum, for use in operations on the head, neck and thorax. During the 1920s and 1930s, other rectal anaesthetic agents were introduced, first paraldehyde, which was discarded because of its unpleasant odour and occasional production of violent restlessness, and then avertin (Eicholz, 1926). This last rectal anaesthetic was still in use and very popular up to the beginning of the last World War, and thus we now had the rectal route of administering an anaesthetic—a route which is still commonly used today, although the vehicle may have changed somewhat. Anaesthesia, it may be said, had turned to the rectum.

In 1891, Quincke described the passage of a hollow needle into the subarachoid space. Thus lumbar puncture became a practical procedure, and it was not long before cocaine was given by this route as an analgesic agent for operations. Owing, however, to the toxicity of cocaine this procedure was soon abandoned, but when Meischner discovered and described percaine (now known as nupercaine) it was used by the spinal route—firstly by Howard Jones—as an analgesic agent. Thus the spinal route for surgical analgesia was established and anaesthesia had taken another turn: spinal analgesia had given it a stab in the back! Surgery in the meantime continued to get bolder and was demanding new techniques from the anaesthetist.

In 1878 Macewen introduced an *intratracheal catheter* by the mouth and started what was to become one of the most important technical changes in the history of anaesthetics. Years later, in 1912, Kelly, of Liverpool, modified an apparatus designed by Elsberg in New York, and used intratracheal insufflation of ether for anaesthesia in his surgical practice. Shipway, of Guy's Hospital, again improved this apparatus to allow the ether to be warmed up and so give a higher concentration of the vapour in the anaesthetic mixture. The Shipway's apparatus was still a familiar sight in most theatres before the last World War, when Boyle, of St. Bartholomew's Hospital, designed his apparatus. Today there can hardly be a hospital in South Africa which does not use one of these machines.

We now have come to the mechanical administration of the inhalational anaesthetic; but, to come back to Macewen and his intratracheal catheter, it was left to Rowbotham in America and Magill in England to perfect the intratracheal technique as we know it today. Magill, especially with his blind intubation and controlled or assisted respiration, made a wonderful contribution to anaesthesia in particular, and the saving of lives in general.

In 1923 Waters, of Wisconsin, demonstrated that carbon dioxide could be absorbed by soda lime in a closed-circuit anaesthetic technique. With this technique, he introduced cyclopropane to anaesthesia; in 1925, Henderson and Haldane introduced carbon dioxide as a gas to be used in anaesthesia; and thus the face of anaesthesia received the new technique of CO_2 absorption and the blast of two new gases.

In 1932, Weese and Scharpff introduced evipan, an intravenous anaesthetic agent, and thereby opened the long-sought-after and entirely new route for the administration of an anaesthetic. Those of us who are young enough to remember this event, will also remember the stir it caused at the time. The surgeon could now promise his patient just a little prick and then sleep! Most of us, however, had a very great respect for evipan, because the fact that once in the vein it could not be withdrawn again, coupled with reports of very marked respiratory depression, made us cautious of the drug. Two years later, Lundy introduced pentothal sodium, stating that it had none of the disadvantages of evipan, and thereby started a new fashion in anaesthesia that was to sweep the world. Unfortunately, the popularity of this agent, and its unbridled use by the uninitiated, led to many unnecessary fatalities. The regrettable tendency of some enthusiasts to embark on the wholesale use of a new drug and a new method, without due regard to aspects of safety, often cause the tragic results of poor judgment to be attributed to the drug or to the method, in general terms. Some of the prejudices about pentothal which sprang from its early misuse, are even today harboured by some members of the profession who should be better informed. Anyhow, pentothal gave the changing face of anaesthesia a shot in the arm!

Then, in 1942, Griffith and Johnson made the discovery that curare, an extract of a South American shrub, could be used as a muscle relaxant in anaesthesia. This brought about another major change in anaesthetics; whereas one had before to rely on a deep level of anaesthesia for relaxation during surgery, one could now keep the patient on a lighter plane and use a muscle relaxant to give the desired relaxation. Curare was followed by the synthetic relaxants and also by the shorter-acting relaxants. The many and varied uses of these drugs have only been fully understood during the last decade, and they have been a boon to the anaesthetist. Here again, as with pentothal, the misuse of these drugs by the unwary and inexperienced led to unnecessary tragedies. The relaxants—and pentothal—spelt the doom of chloroform, which had been known for years to have many disadvantages but was still used, purely for its ease of induction and relaxant qualities. These two activities were now taken over by pentothal and the relaxants, and chloroform disappeared from the general scene, although it is still used in midwifery.

In 1942 Allen made the first reports on hypothermia in anaesthetics. Although this technique has had many setbacks, mainly owing to the ventricular fibrillation it sometimes produces, it is still used successfully in combination with other techniques in major operations.

Then came along induced and controlled hypotension. The surgeons had for years been complaining that during some types of surgery the bleeding at the site of operation hindered their work. Scurr was the first in this field, and in 1949 he used pentamethonium halide (lytensium) to reduce the blood pressure during operations. Enderby and Wyman continued the work with these sympatholytic agents and hexamethonium bromide (vegalysin) became more popular because of its more constant action. Then Randall, and some others, described arfonad—a thiophanium derivative. As the result of the work of Sarnoff, Scurr and Wyman during the early fifties, this agent came to be used practically exclusively; it had fewer complications or side-effects than the ganglion-blocking agents, and was more constant in its action. Controlled hypotension is a very useful technique in anaesthesia widely practised today, but one must utter a word of warning—to embark upon this procedure, which after all is highly unphysiological, without proper selection of the case and proper after-care organization, is to court disaster. Apart from all other complications, and there are many, primary heart failure is an ever-present danger with this technique. As A. R. Hunter put it, this technique should be confined to those cases where it makes the impossible possible, and it should not be used to make the possible easy.

During the last decade, thoracic surgery took a dramatic turn with the invention of the heart-lung machine, and entirely new fields were opened to the surgeon. Hand in hand with this development went that in anaesthesia, with relaxants, controlled respiration, and a light plane of anaesthesia. One feels that this technique, plus a certain amount of hypothermia, will probably be the accepted practice for these operations before long. Be that as it may, the success this highly technical procedure has met with, as indicated by the comparatively large number of patients who have been turned into useful human beings from human wrecks, is beyond all expectations and the procedure has certainly come to stay. The one fact brought out is that in these complicated surgical undertakings teamwork is a *sine qua non*, and that it is around this essential that success or failure to a great extent hinges.

In this brief review I have purposely left out a number of anaesthetic agents which made very little difference to the progress of anaesthesia—ethyl chloride, vinesthene, trichlorethylene, viadril, and halothane—to mention but a few. The last mentioned is important, however, in that it is a very potent, non-irritant, non-inflammable drug. It is best administered in very carefully regulated percentages and for that purpose several apparatuses have been designed to ensure an accurate percentage flow of vapour—shades of Snow's chloroform apparatus of nearly a century ago! Halothane has found a permanent place in the anaesthetist's armamentarium until a less potent drug with all its essential qualities comes along. In viadril we have a completely new source for an anaesthetic agent, namely the steroids. This agent was thoroughly tested at various hospitals—at Pretoria General Hospital by Kok and Knipe—and, although it has not found a permanent place in the anaesthetist's drug cupboard, the source of this agent warrants further exploration.

Furthermore, I have not mentioned the various drugs now available for premedication and post-operative medication. There are a number of newer ones that will stay with us for quite a while but I think atropine will stay the longest, being, to my mind, the most important one of any real benefit.

The nonchalance with which the tiro disregards what is to him the minor matter of premedication sometimes astounds one. I have seen colleagues sail into an unexamined and unpremedicated case with the greatest abandon—and then blame the apparatus or drug for the resulting fiasco.

Resuscitation of the patient in cardiac arrest by means of cardiac massage made a dramatic entry into anaesthetic practice, and the daily papers still make a great display of cases of this kind; and now the electric defibrillator and pacemaker for the ventricle with a bundle of Hiss that will not behave has entered the realm of the anaesthetist.

Since the last war, blood transfusion, and the intravenous drip with or without various serum substitutes or plasma expanders, have also become commonplace in anaesthesia and nowadays one never sees an operation of any magnitude without the anaesthetist's manipulating one of these bits of apparatus. Venipuncture has become the commonest procedure for the anaesthetist and woe betide the practitioner who is clumsy in this department of his practice.

Hypnosis, to create insensibility for surgical procedures, has been tried successfully for many years now. For years too, the psychiatrists have been creating a state of unconsciousness in their patients by passing an electric current through the brain—a procedure called electronarcosis, which I have been told is used fairly extensively in Russia for operations. The obvious limitations of these two techniques, however, have kept them out of the field of general anaesthetic practice so far.

SUMMARY AND CONCLUSION

As I now come to the end of this brief and quite inadequate review, it is just as well to stop and look back on the changing face of this fascinating subject. We started off with our inhalational methods and drugs through gas, ether, ether and chloroform. Then came the rectal route, the spinal route, hypothermia and finally the intravenous route, with the still untried electric shock through the brain in the offing. Hand in hand went the new techniques of intratracheal, semi-closed and closed circuit, with carbon-dioxide absorption, controlled respiration and hypotension. All this brought along new drugs and gases, some to be discarded after very short use, others to find a permanent place in the field of anaesthesia. New and elaborate pieces of apparatus were designed and put into use for all this development and, one may honestly say, for the good of the patient. But if you or I were to be asked to give an anaesthetic in a real emergency today, with the least material at our disposal, what would be the absolute minimum we should require? My answer would be—a Schimmelbusch mask and a bottle of ether. Now, as a parting shot may I ask, does the medical student of today receive enough training in this basic art of the subject?

BRITISH MEDICAL ASSOCIATION

SIR CHARLES HASTINGS AND CHARLES OLIVER HAWTHORNE CLINICAL PRIZES, 1961

These prizes, for the promotion of systematic observation, research and record in general practice, are respectively of £75 and £50 in value. Any member of the British Medical Association engaged in general practice is eligible to compete.

Entries must consist of original and unpublished material and preliminary notice of entry is required. Forms and further particulars may be obtained from the Secretary, BMA House, Tavistock Square, London, W.C.1.

The closing date for entries is 30 November 1960.

FARMASEUTIESE NUUS : PHARMACEUTICAL NEWS

ROCHE PRODUCTS (PTY.) LTD.—APPOINTMENT OF MEDICAL ADVISER

Roche Products, Johannesburg, take pleasure in announcing the appointment of Dr. W. E. J. Leigh as medical and scientific adviser to their company.

Dr. Leigh matriculated in South Africa. He later studied medicine at the University of the Witwatersrand and graduated as an M.B., B.Ch. It is of interest that he obtained first-class honours, amongst others, in the subject of pharmacology. He completed his medical and surgical housemanship at the General Hospital, Johannesburg. Thereafter he was associated with the Transvaal Chamber of Mines in experimental clinical work on the uranium workers at the Cottesloe Hospital.

Whilst in private medical practice he served on the panel of medical operators of the South African Blood Transfusion Service for some time. At a later stage Dr. Leigh accepted a Union Health Department appointment, which he held until he joined the company.

The closest liaison between the medical profession and the pharmaceutical houses has become a necessity owing to the great scientific developments which have taken place, and it was therefore felt that the appointment of a qualified medical doctor to Roche Products—a long-established practice in the United Kingdom, Europe and the United States—would be essential, although it is a fairly new venture in the Union of South Africa.

Dr. Leigh's activities will consist mainly of the planning and institution of clinical trials on preparations which are as yet in the research stage. The Union is in many ways uniquely placed for this type of scientific work; firstly, on account of its climate and geographical position (for instance when it concerns the therapy of parasitological disorders), and secondly, on account of its excellent universities, and hospital system and the great number of exceptional medical scientists who have gathered for work in this country.

Another facet of Dr. Leigh's activity will be the detailed study of the clinical aspects and pharmacology of preparations

which will put him in a position to give any information which may be required, and even advice on a high scientific level.

Roche Products feel that doctors in the Union would be keenly interested in contributing to the type of clinical research done by medical men in other countries where medical opinion is formed.

Dr. Leigh will fill the need for a liaison officer qualified to deal with all aspects of scientific significance and local planning of clinical research.

GLAXO-ALLENBURYS (S.A.) (PTY.) LTD.

The Directors of the associated companies, Glaxo Laboratories (S.A.) (Pty.) Ltd. and Allen & Hanburys (Africa) Ltd., announce that from 1 July 1960 their activities will be merged into a combined company trading as Glaxo-Allenburys (S.A.) (Pty.) Ltd. with addresses at Manchester Road, Wadeville, Transvaal, and 121 Congella Road, Durban.

In the interests of improved services, the Glaxo-Allenburys range of ethical medical specialities will be issued from the Company's establishments at the above addresses. A descriptive list of the combined range of products has been circulated to the medical profession.

The surgical divisions of the Glaxo-Allenburys Company will continue to distribute a full range of surgical instruments, hospital equipment, orthopaedic appliances, operating tables, etc. from their present establishments in Johannesburg, Cape Town, and Durban.

The Directors are confident that the combined and coordinated efforts of their medical, pharmaceutical and surgical representatives will enable the Glaxo-Allenburys organization to offer improved standards of service throughout the Union of South Africa.

IN DIE VERBYGAAN : PASSING EVENTS

Dr. Jack Levin, anaesthetist, formerly of 901 Medical Centre, Cape Town, has joined Drs. Abelsohn, Smiedt and Jenkin in their practice at 611 Medical Centre, Cape Town. Dr. Levin was formerly first assistant at St. George's Hospital, London; Registrar at the Great Ormond Street Hospital for Sick Children, London; and Research Assistant to Mr. Wyllie McKissock at the Atkinson-Morley Neurosurgical Unit, London. Dr. Levin's telephone numbers will remain unchanged: Rooms 3-1256, residence 5-2138.

Dr. Jack Levin, narkotiseur, voorheen van Mediese Sentrum 901, Kaapstad, het by drs. Abelsohn, Smiedt en Jenkin aangesluit in hul praktyk te Mediese Sentrum 611, Kaapstad. Dr. Levin was voorheen hoofassistent aan die St. George-hospitaal, Londen; Registrateur aan die ‚Great Ormond Street Hospital for Sick Children', Londen; en Navorsingsassistent vir dr. Wyllie McKissock aan die Atkinson-Morley Neurochirurgiese Eenheid, Londen. Dr. Levin se telefoonnommers bly onveranderd: Spreekkamer 3-1256, woning 5-2138.

* * *

South African Institute for Medical Research, Johannesburg, Staff Scientific Meeting. The next meeting will be held on Monday 4 July at 5.10 p.m. in the Institute Lecture Theatre. Dr. H. Festenstein will speak on 'Immunological tolerance and microbiological antigens'.

Afdeling Potchefstroom, Tak Suid-Transvaal (*M.V.S.A.*). 'n Kliniese vergadering van hierdie Afdeling sal gehou word te Klerksdorp Hospitaal op Maandag 4 Julie om 8 nm. Dr. W. P. U. Jackson, van die Departement van Interne Geneeskunde, Groote Schuur Hospitaal en die Universiteit van Kaapstad, sal die vergadering toespreek oor ‚Prediabetes—die diagnose, kliniese beeld en verwantskap tot swangerskap'.

Potchefstroom Division, Southern Transvaal Branch (*M.A.S.A.*). A clinical meeting of this Division will be held at the Klerksdorp Hospital on Monday 4 July at 8 p.m. Dr. W. P. U. Jackson, of the Department of Medicine, Groote Schuur Hospital, and the University of Cape Town, will address the meeting on 'Prediabetes —its recognition, its clinical manifestations and its relation to pregnancy'.

* * *

Ophthalmological Society of South Africa (*M.A.S.A.*). Prof. J. Francois, a visiting ophthalmologist from Ghent, Belgium, will address two meetings of the Society. Both lectures will take place in the Harveian Lecture Theatre, Medical School, Johannesburg, commencing at 8.15 p.m.

Monday 4 July 1960: 'The value of electro-retinography for the diagnosis of congenital blindness'.

Friday 8 July 1960: 'Gene carriers in ophthalmology'.

All medical practitioners are welcome to attend the lectures.

NUWE PREPARATE EN TOESTELLE : NEW PREPARATIONS AND APPLIANCES

LAEVOSAN

Westdene Products (Pty.) Ltd. announce the introduction of Laevosan, manufactured by Calmic, of England, and supply the following information:

Laevosan is a 20% solution of laevulose (fructose) presented in ampoule form for intravenous injection. Laevulose has many advantages over glucose as carbohydrate supportive therapy in conditions of metabolic stress. Owing to new and more economical methods of processing, this useful carbohydrate is now available for general clinical use.

Laevulose enters the energy-releasing system more directly than glucose and is metabolized independently of insulin. Where the liver synthesizes only 12% of glycogen from glucose, it synthesizes 35 - 40% from laevulose. Furthermore, the severely damaged liver is still capable of utilizing laevulose when it can no longer utilize glucose.

Laevosan has a protein-sparing action in cases of traumatic shock or severe infection. It is also indicated for acute and chronic hepatitis, toxaemias of pregnancy, irradiation sickness, etc. High concentrations may be injected with little risk of vein damage.

Laevosan is available as a sterile pyrogen-free solution containing 20% laevulose. It is supplied in boxes containing five 10 c.c. ampoules. Further details may be obtained from the sole South African distributors, Messrs. Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

DUVADILAN

South African Druggists Limited are shortly to introduce Duvadilan (isoxsuprine HCl, a p-oxy-ephedrine derivative) manufactured under licence from Philips-Duphar, of Amsterdam, by the Lennon Limited Laboratories at Port Elizabeth. This product has been used overseas since 1955.

Composition. Duvadilan is 1-(p-hydroxy-phenyl)-2-(1′-methyl-2′phenoxyethylamino) propanol-hydrochloride. It is a synthetic compound related to ephedrine and adrenaline.

Mode of action. Duvadilan acts directly as a smooth-muscle relaxant, with selectivity of action on blood vessels, uterus, and bronchial musculature. Vasodilation is *not* achieved through adrenergic blockade.

Indications. Duvadilan has been extensively shown to be an 'excellent', 'highly effective', 'valuable' and 'even striking' vasodilator without distressing side-effects (hypotension, tachycardia) when correctly administered. It is suggested that Duvadilan will be 'well suited to out-patient and office management of peripheral vascular disease'.

Duvadilan has proved to be an effective vasodilator in cases that have shown no improvement on other vasodilator therapy. 'Dramatic results' have also been obtained with Duvadilan in its role as a myometrial relaxant.

Dosage and side-effects. Duvadilan may be given both orally and parenterally, and it has been found useful to start treatment by giving intramuscular injections and tablets simultaneously, and later on withdrawing the injections and maintaining the patient on tablets. Thus a combination of 1 ampoule every other day (10 mg.) and 2 - 4 tablets (20 - 40 mg.) daily has proved to be an effective schedule to start treatment.

It is frequently emphasized in the literature that, when administered as recommended, there are no distressing side-effects to Duvadilan therapy. So-called 'palpitations' when encountered,

have proved to be manifestations of increased cardiac output (stroke) rather than tachycardia.

Packings. 2 c.c. ampoules containing 10 mg. of Duvadilan in boxes of 6. Tablets containing 10 mg. of Duvadilan in bottles of 100 and 500.

Further information and samples for clinical evaluation may be had from Ethical Promotion Section, South African Druggists Limited, P.O. Box 5644, Johannesburg, or upon request to any wholesale branch of the company.

ALTAFUR

SKF Laboratories (Pty.) Ltd. introduce Altafur Tablets (furaltadone), a new chemotherapeutic agent, and supply the following information:

Formula. Altafur contains 3-(5-nitro-2-furfurylideneamino)-5-(4-morpholinomethyl)-2-oxazolidone.

Indications. Altafur is a newly synthesized, bactericidal, broad-spectrum chemotherapeutic agent for systemic use. It has proved successful in treating a wide variety of conditions, including pulmonary infections, abscesses, cellulitis, pyodermas, septicaemia, and various wound infections. Its outstanding merit lies in a capacity to treat infections caused by staphylococci, whether or not resistant to other antibacterial agents.

There are no contra-indications.

Side-effects and special considerations. Altafur occasionally causes anorexia, heart-burn and flatulence and very rarely nausea and vomiting. Such side-effects can be overcome by taking the drug with food or milk. A maculopapular cutaneous eruption has been reported very occasionally and has disappeared when the drug has been stopped. No other side-effects have been reported. Alcohol should be forbidden during treatment with Altafur, since in sensitive patients it may result in dyspnoea, constriction in the chest, and sometimes an erythema. In rare cases darkly coloured metabolites of Altafur are excreted in the urine. These are quite harmless.

Dosage. The average adult dose of Altafur is one 250 mg. tablet 4 times a day with meals, and with food at bedtime. Dosage is calculated according to the following formulae: Infants and younger children, 10 - 11·5 mg. per lb. body-weight per day; and older children and adults, 7 - 10 mg. per lb. body-weight per day.

The tablet may be finely crushed and given in a teaspoonful of food or milk if desired—a method which may be more suitable for children. For severe staphylococcal infections the dosage may be increased to about 13·5 mg. per lb. body-weight, per day, given in 4 equally divided doses. Treatment is usually required for from 5 to 7 days, though it may be more prolonged in severe or complicated infections such as osteomyelitis, septicaemia, or endocarditis. There are no known contra-indications to concomitant therapies.

Presentation. Altafur is available as green 250 mg. tablets in containers of 20 and 200. Sensi-discs for sensitivity tests are available from SKF on application.

Further information may be obtained from SKF Laboratories (Pty.) Ltd., P.O. Box 784, Port Elizabeth.

BOEKBESPREKINGS : BOOK REVIEWS

MEMORY AND LEARNING

Brain Memory Learning. A Neurologist's View. By W. Ritchie Russell, *C.B.E.*, M.D. (Edin.), D.Sc. (Oxon), F.R.C.P. (Edin. and Lond.). Pp. ix + 140. 12 figures. 18s. London, New York and Toronto: Oxford University Press. 1959.

The mind is dependent on the coordinated activity of the 10,000 million cells which constitute the central nervous system. Each one of these cells has very complex synaptic connections, so that a group of neurones is subjected to influences from distant cell-groups, as seen in the following example: The cerebral cortex is affected by the reticular formation in the brain stem. Influences from these deeper reticular areas result in an alerting response, reducing cortical thresholds and thus increasing attention (the startle response). Furthermore, activity enhances the functional effectiveness of synapses, so that an action which has been done before can be more easily done again.

The author presents this neurological knowledge as the physiological basis of memory and learning. He discusses the phantom-limb phenomenon, in which an amputated limb is still 'felt' to be present. Hallucinations, dreaming, and visual imagery, are held to depend on activity of the parieto-occipital region of the brain. Discussion of epilepsy, concussion, frontal-lobe injury, pain attention, and the traumatic amnesias, provides further basis for a physiology of 'psychological' processes.

A defect of this presentation is the author's limitation in grasping the range and complexity of psychological phenomena. Schizophrenia 'certainly suggests a physiological confusion in some of the cerebral mechanisms', thought by the author to rest on a physiological mechanism in early childhood, for identification of which he looks to 'the psycho-analysts'. As uninformed appears his grasp of the realities of child-rearing and personality formation when he says that in any conflict over two possible reactions, 'what is actually done is determined finally by a numerical superiority of nerve cells tending to act in one direction . . . '. Motivation itself becomes located in the nerve cells. This brain language into which psychic events are translated reaches such extremes that so abstract a concept as the super-ego itself becomes firmly identified with the frontal lobes, and is materialized in 'an army of nerve cells'.

Clearly, impressive though knowledge about the neurological basis of human behaviour already is, the author does not succeed in expressing psychological experience in terms of physical mechanisms. While mind is dependent on brain, mind cannot be understood in physiological terms. The author recognizes this in such statements as this: 'No doubt the efficiency with which the frontal armies are arrayed varies greatly according to previous experience . . . '. It is this previous experience of the individual as a determinant of behaviour which the author fails to comprehend and which cannot be expressed in such neurophysiological concepts as 'facilitated circuits'. On his own neurological ground the author provides a great deal of fascinating information, much the outcome of his own outstanding research into the clinical effects of brain lesions. H.W.

THE MEDICAL ANNUAL

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Edited by R. Bodley Scott, M.A., D.M., F.R.C.P. and R. M. Walker, M.S. (Lond.), F.R.C.S. Pp. xl + 620 + 19. Illustrations. Bristol: John Wright & Sons Ltd. 1959.

This 77th issue of the well-known *Medical Annual* continues to maintain its position as a year book of medical and surgical practice. This year Sir Henry Tidy has retired from the editorship, which he has held since 1934; and 3 former contributors to the medical section—Sir Philip Manson-Bahr, Dr. Stanley Banks and Dr. J. W. McLaren—have also retired.

Three well-written and stimulating special articles—'New sex hormone preparations (progestogens)', 'Cross infections in the ward,' and 'Emphysema'—are presented. Another informative article deals with 'Cancer research', which should interest all medical readers. Reference is also made to the recent prophylactic use of 'hyper-immune gamma globulin' (HGG.) during the surveillance of smallpox contacts. It is hoped that it will prove of value in contacts seen too late for prophylactic vaccination.

Surprisingly enough, nothing appears this time on the greatest of killers—malaria. There is surely a vast amount of research on malaria being carried out all over the world. Readers would appreciate reviews on this, on the newer remedies, and on the subclinical effects of the malady. Another item that would be welcomed is a review on that most treacherous disease condition, pulmonary embolism.

G. C. A. vd W.

REWARDS OF MEDICINE

The Rewards of Medicine and Other Essays. By Hugh Barber. Pp. vi + 140. 15s. net. London: H. K. Lewis. 1959.

Readers who enjoyed Dr. Barber's earlier collection of essays in *The Occasion Fleeting* will derive the same pleasure in *The Rewards of Medicine.* Most of these essays have appeared in *Guy's Hospital Gazette*, but I have no doubt that the many who do not see the *Gazette* will welcome their appearance in this form. I certainly have. A.H.T.

THE STAPHYLOCOCCUS

Staphylococcal Infections. By Ian Maclean Smith, M.D., Ch.B., F.R.F.P.S.G. Pp. 180. 6 figures. $4.25. Chicago: Year Book Publishers, Inc. 1958.

The prevalence of staphylococcal infections and the increasing difficulty in curing them is a matter of concern to physicians and surgeons. While the recognition of staphylococcal infections is not usually difficult, physicians should whenever possible verify their clinical impression. In this useful book the gist of the bacteriology, strains, toxins, and the control of staphylococcal infections in hospitals is briefly and neatly described. The questions of isolation, hand-washing, carriers (the main area for growth is the human nose), wound dressing, operating-room technique, ward administration and housekeeping are discussed, and the consideration of the cost of infection and the price of control. The indiscriminate use of antibiotics is condemned. While it is to be lamented that there is no single effective treatment to be used in all cases, there are measures described for the cure of many patients with severe staphylococcal disease. This handy volume brings together much of the knowledge on the subject and indicates where further knowledge is required.

N.S.

BOEKE ONTVANG : BOOKS RECEIVED

Variations on a Theme by Sydenham—Small-pox. By P. B. Wilkinson, M.R.C.P. Pp. 40. 69 illustrations. 17s. 6d. + 1s. postage. Bristol: John Wright & Sons Ltd. 1959.

Surgical Note-taking. A booklet for surgical dressers and clerks commencing clinical studies. 5th edition. By Charles F. M. Saint, *C.B.E.*, M.D., M.S., F.R.C.S. (Eng.), F.R.A.C.S. (Hon.) and Jan H. Louw, Ch.M. Pp. viii + 172. 12s. 6d. net. London: H. K. Lewis & Co. Ltd. 1960.

Consequences of Disturbance: The Pest Situation Examined. By Alan Mozley, D.Sc., Ph.D., F.R.S.E. Pp. x + 61. 9s. net. London: H. K. Lewis & Co. Ltd. 1960.

The Aetiology and Arrest of Pre-eclamptic Toxaemia with Early Ambulant Treatment. By K. Douglas Salzmann, M.D., M.R.C.P. (Ed.), D.Obst. R.C.O.G. Pp. viii + 69. 1 illustration. 10s. 6d. Net. London: H. K. Lewis & Co. Ltd. 1960.

Pressure Group Politics—The Case of the British Medical Association. By Harry Eckstein. Pp. 168. 16s. net. Cape Town. Howard B. Timmins (Pty.) Ltd. 1960.

Physiology of the Retina and the Visual Pathway. By G. S. Brindley, M.A., M.D. Pp. xi + 298. Illustrated. 35s. net. London: Edward Arnold (Publishers) Ltd. 1960.

Brucella Infection and Undulant Fever in Man. By Sir Weldon Dalrymple-Champneys Bt., *C.B.*, D.M., D.P.H., F.R.C.P. Pp. 196. 20 illustrations. London, New York, Toronto: Oxford University Press. 1960.

Encyclopedia of Medical Syndromes. By Robert H. Durham, M.D., F.A.C.P. Pp. xiv + 628. $13.50. New York: Paul B. Hoeber, Inc. 1960.

Requirements for Biological Substances: 1. *General requirements for manufacturing establishments and control laboratories;* 2. *Requirements for poliomyelitis vaccine (inactivated)*. Report of a Study Group. Technical Report Series No. 178. Pp. 30. 1s. 9d. Also available in French and Spanish. Local sales agent: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724, Pretoria. Geneva: World Health Organization. 1959.

Effect of Radiation on Human Heredity: Investigation of Areas of High Natural Radiation. First Report of the Expert Committee on Radiation. Technical Report Series No. 166. Pp. 47. 1s. 9d. Also available in French and Spanish. Local sales agent: Van Schaik's Bookstore (Pty.) Ltd., P.O. Box 724, Pretoria. Geneva: World Health Organization. 1959.

Medical Helminthology. By J. M. Watson, D.Sc. (Lond.), A.R.C.S. Pp. 500. 62 pp. of illustrations incorporating over 600 individual drawings. 84s. + 2s. 9d. postage. London: Baillière, Tindall & Cox Ltd. 1960.

The Triumph of Surgery. By Jürgen Thorwald, translated from the German by Richard and Clara Winston. Pp. 483. 25s. net. London: Thames and Hudson. 1960.

Menslike Fisiologie. Dele I en II. 3de uitgawe. Deur H. E. Brink, D.Sc. (Stell.). Pp. 606 en 477. Geïllustreerd. Deel I 57s. 6d. Deel II 42s. Stellenbosch/Grahamstad: Die Universiteits-Uitgewers en -Boekhandelaars. 1960.

Radiation Hygiene Handbook. A practical reference covering the industrial, medical, and research uses of radiation and atomic energy with special applications to the fields of health physics, industrial hygiene, and sanitary engineering. 1st edition. Editor-in-Chief: Hanson Blatz. In 23 sections. $27.50. Local agent: Medical Book Department, Westdene Products (Pty.) Ltd., 23 Essanby House, 175 Jeppe Street, Johannesburg, and at Cape Town and Durban. New York, Toronto, London: McGraw-Hill Book Company, Inc. 1959.

Leukocyte Antigens and Antibodies. By Roy L. Walford, M.D. Pp. ix + 182. $6.75. New York and London: Grune & Stratton, Inc. 1960.

The Haemolytic Anaemias. Congenital and Acquired. *The Congenital Anaemias*. 2nd edition. By J. V. Dacie, M.D. (Lond.), F.R.C.P. (Lond.), Pp. vii + 399. 118 illustrations. 45s. net. London: J. & A. Churchill Ltd. 1960.

The Cell of Schwann. By Gilbert Causey, M.B., F.R.C.S. Pp. xi + 120. 40 figures. 21s. net + 1s. postage abroad. Edinburgh and London: E. & S. Livingstone Ltd. 1960.

A Short Synopsis of Human Protozoology and Helminthology. By L. R. S. MacFarlane, *O.B.E.*, M.D., M.A., D.P.H., Brigadier. Pp. vii + 251. 61 figures. 35s. net + 1s. 5d. postage abroad. Edinburgh and London: E. & S. Livingstone Ltd. 1960.

The Essentials of Perimetry. By Howard Reed, M.B., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.S.(C), F.A.C.S. Pp. xi + 192. Illustrated. 45s. London, New York, Toronto: Oxford University Press. 1960.

The Biochemical Response to Injury. A Symposium organized by the Council for International Organizations of Medical Sciences. Edited by H. B. Stoner with the assistance of C. J. Threlfall. Pp. xi + 467. Illustrated. 57s. 6d. Oxford: Blackwell Scientific Publications Ltd. 1960.

The Treatment of Bronchial Neoplasms. By Robert R. Shaw and Donald L. Paulson, M.D. with a chapter on *Bronchial Adenoma* by John Lester Kee, Jr., M.D. Publication Number III in the John Alexander Monograph Series on Various Phases of Thoracic Surgery. Pp. x + 135. Illustrated. 64s. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1959.

Cinefluorography. Proceedings of the First Annual Symposium on Cinefluorography, sponsored by the Department of Radiology, University of Rochester, School of Medicine and Dentistry, New York, Friday and Saturday, November 14 and 15, 1958. Edited by George H. S. Ramsey, M. D.; James S. Watson, Jr., M.D.; Theodore A. Tristan, M.D.; Sydney Weinberg; and William S. Cornwell, M.A. Pp. xvi + 266. Illustrated. 94s. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Modern Nursing. Theory and Practice. By Winifred Hector. Pp. vii + 515. 145 figures. 30s. net. London: William Heinemann Medical Books Ltd. 1960.

The Older Patient. By 21 authors. Edited by Wingate M. Johnson, M.D. Pp. xiv + 589. Illustrated. $14.50. New York: Paul B. Hoeber, Inc. 1960.

Management of the Aged Surgical Patient. By Sidney E. Ziffren, M.D. With chapters on *Anesthesia* by Stuart C. Cullen, M.D. and *Urology* by Rubin H. Flocks, M.D. and a discussion of *The Cardiac and Diabetic Patient Facing Emergency Operation* by Raymond F. Sheets, M.D. Pp. 219. 30 figures. $7.50. Chicago: The Year Book Publishers, Inc. 1960.

Childbirth without Fear. 4th edition. By Grantly Dick-Read, M.A., M.D. (Cantab.). Pp. xv + 266. 12s. 6d. London: William Heinemann Medical Books Ltd. 1960.

Medical Terminology for Radiographers. By Paul M. Davies, M.B., B.S., D.P.H., F.F.R., D.M.R. Pp. 242. 15s. net. London: William Heinemann Medical Books Ltd. 1960.

Textbook of Gynaecology. 5th edition. By J. H. Peel, M.A., B.M., B.Ch. (Oxon), F.R.C.S., F.R.C.O.G. Pp. xv + 491. 209 figures. 30s. net. London: William Heinemann Medical Books Ltd. 1960.

The Year Book of Radiology, 1959 - 1960. Radiological Diagnosis. Edited by John Floyd Holt, M.D. and Walter M. Whitehouse, M.D. *Radiation Therapy.* Edited by Harold W. Jacox, M.D. and Morton M. Kligerman, M.D. Pp. 446. 328 figures. $10.50. Chicago: The Year Book Publishers, Inc. 1960.

Bibliography of Cancer Produced by Pure Chemical Compounds. A survey of the literature up to and including 1947. By Otto Neubauer, M.D. Pp. xxvii + 604. English price 42s. London: Oxford University Press. 1959.

The Arterial Wall. Edited by Albert I. Lansing, A.B., Ph.D. Sponsored by The Gerontological Society, Inc. Pp. 260 + ix. 17 pages of illustrations. 60s. + 2s. 6d. postage. London: Baillière, Tindall and Cox Ltd. 1959.

Progress in the Biological Sciences in Relation to Dermatology. Edited by Arthur Rook, M.D., M.R.C.P. Pp. xv + 480. Illustrated. 84s. net. London: Cambridge University Press. 1960.

Clinical Obstetrics and Gynecology, vol. 2, no. 4. *Cesarean Section*, edited by Edwin J. de Costa, M.D. *Advances in Gynecologic Surgery*, edited by S. B. Gusberg, M.D. Pp. 303. Illustrated. Subscription $18.00 a year. New York: Paul B. Hoeber, Inc. 1959.

Hypnotism for Medical and Dental Practitioners. By A. A. Mason, M.B., B.S. With chapters on *Hypnosis in Dental Surgery and Obstetrics* by K. Dawson Watts, F.D.S.R.C.S. (Ed.) and S. D. Perchard, M.D. (Lond.), M.R.C.O.G. Pp. 223. 11 illustrations. English price 30s. net. London: Secker & Warburg. 1960.

On the Causation of Varicose Veins and Their Prevention and Arrest by Natural Means. An evolutionary approach. By T. L. Cleave, M.R.C.P. (Lond.), R.N. Pp. 32. 7s. 6d. + 4d. postage abroad. Bristol: John Wright & Sons Ltd. 1960.

The Newly Born Infant (Paediatric Tutorials). By Andrew Bogdan, M.D., M.R.C.P.E., D.C.H. Pp. 38. 4s. 6d. Published by the author. 1959. Local agent: P. B. Mayer, 902 Norwich House, Heerengracht, Cape Town.

A Handbook of Diseases of the Skin. 6th edition. By Herbert O. Mackey, F.R.C.S.I., L.R.C.P.I., D.P.H. (Univ. Dubl.), L.M., F.R.I.A.M. Pp. 263. 200 illustrations. English price 8s. 6d. London: MacMillan & Co. Ltd. Dublin: C. J. Fallon Ltd. 1959.

Psychiatric Services and Architecture. Public Health Papers No. 1. By A. Baker, R. Llewelyn Davies and P. Sivadon. Pp. 50 3s. 6d. Geneva: World Health Organization. 1959. Local agent: Van Schaik's Book Store (Pty.) Ltd., P.O. Box 724, Pretoria.

Epidemiological Methods in the Study of Mental Disorders. Public Health Papers No. 2. By D. D. Reid, M.D., D.Sc., M.R.C.P. Pp. 79. 5s. Geneva: World Health Organization. 1960. Local agent: Van Schaik's Book Store (Pty.) Ltd., P.O. Box 724, Pretoria.

Health Services in the USSR. Public Health Papers No. 3. Pp. 58. 3s. 6d. Geneva: World Health Organization. 1960. Local agent: Van Schaik's Book Store (Pty.) Ltd., P.O. Box 724, Pretoria.

High Blood Pressure and Pregnancy. By Lance Townsend, M.D., B.S., F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G., D.T.M. & H. Pp. viii + 115. 22 figures and 26 tables. 40s. net. London & New York: Cambridge University Press. 1960.

A Guide to the Identification of the Genera of Bacteria, with methods and digests of generic characteristics. Based on data given in the seventh edition of Bergey's *Manual of Determinative Bacteriology* and on original papers. By V. B. D. Skerman. Pp. ix + 257. 44s. + 2s. 3d. postage. London: Baillière, Tindall & Cox Ltd. Baltimore, Md.: The Williams & Wilkins Company. 1959.

Recent Research in Freezing and Drying. Edited by A. S. Parkes, *C.B.E.*, F.R.S. and Aubrey U. Smith, D.Sc., M.B., B.S. Pp. vii + 320. Illustrated. English price 63s. Oxford: Blackwell Scientific Publications Ltd. 1960.

Sex Differentiation and Development. Memoirs of the Society for Endocrinology No. 7. Edited by C.R. Austin. Proceedings of a Symposium held at the Royal Society of Medicine, London, on 10 and 11 April 1958. Pp. x + 198. Illustrated. London: Cambridge University Press. 1960.

Clinical Physiology. Edited by E. J. Moran Campbell, B.Sc., Ph.D., M.D., M.R.C.P. and C. J. Dickinson, B.A., B.Sc., B.M., M.R.C.P. Pp. xi + 530. Illustrated. English price 50s. Oxford: Blackwell Scientific Publications Ltd. 1960.

British National Formulary 1960. Standard edition. Published jointly by the British Medical Association and the Pharmaceutical Society of Great Britain. Pp. 272. English price 7s. 6d., interleaved 11s. 6d. Obtainable from A.P.S. Journal (Pty.) Ltd., P.O. Box 6290, Johannesburg. London: The Pharmaceutical Press. 1960.

Babies and Young Children. Feeding: management: care. 2nd edition. By Prof. Ronald Illingworth and Dr. Cynthia Illingworth. Pp. vii + 331. 24 photographs and 50 pen sketches. English price 18s. net. London: J. & A. Churchill Ltd. 1960.

BRIEWERUBRIEK : CORRESPONDENCE

OCCLUSION OF THE SUPERFICIAL FEMORAL ARTERY

To the Editor: In their article 'Occlusion of the superficial femoral artery',[1] published in the *Journal* of 4 June, Messrs. Max Lautré and Len Stein make the following statement: 'Arteries above the inguinal ligament are generally of large enough lumen to allow of disobliteration by thrombo-endarterectomy. We cannot agree with the findings of Louw and Blumberg, who describe poor results in such vessels'. They refer to an article[2] by us published in the *Journal* of 11 July 1959 in which we state: 'We tried the operation of thrombo-endarterectomy in 3 of our cases for removal of localized segmental blocks in the common iliac, femoral and popliteal, but in none was the procedure successful, and at the present time we regard "bypass" as the operation of choice'.

I should like to point out that 'at the present time' indicated about the middle of 1958 when the manuscript was prepared. There is an addendum to this article which was submitted for publication in December 1958, as stated in the *Journal*, in which we reported 2 cases of successful thrombo-endarterectomy for short segmental obstruction, involving aortic bifurcation and common iliac arteries.

In the Correspondence Columns[3] of the *Journal* of 22 August 1959 I made the following statement: 'A considerable number of endarterectomies have now been done for aorto-iliac occlusions with most promising results, and we now feel that the procedure has a very definite place in the treatment of arterial occlusions, particularly if it is limited to the more proximal larger vessels'. From the above it should be clear that our views have been misrepresented, because, in the first place, we did not condemn thrombo-endarterectomy for large vessels, and merely stated that in 3 cases, 2 of which had occlusions below the groin, our results had been poor; and in the second place, we took the trouble to mention in our addendum and in a subsequent letter, that we considered thrombo-endarterectomy a very useful procedure.

In this connection I should like it to be known that I have just received the galley-proofs of our most recent article on this subject, in which we make the following statement in regard to thrombo-endarterectomy: 'Extremely good results can be expected in all patients presenting with a limited area of stenosis or occlusion, and this applies both to the carotid arteries and the large arteries supplying the lower limbs'. 'Because of the better long-term results following endarterectomy, we feel that this operation should be employed more frequently in the thigh . . . '. To date we have performed endarterectomies on 88 patients for occlusive arterial disease (61 aorto-iliac, 12 femoro-popliteal, 14 carotid and 1 renal). It is this experience which has convinced us that the operation is followed by excellent results and is, *at present* the procedure of choice in most cases.

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10 June 1960

1. Lautré, M. and Stein, L. (1960): S. Afr. Med. J., 34, 474.
2. Louw, J. H. and Blumberg, L. (1959): *Ibid.* 33, 576.
3. Correspondence (1959): *Ibid.*, 33, 716.